Kelly, T. E., 32
Kennedy, J. H., 76
Killough, John H., 352
Kimsey, Jean A., 570
Kincaid, O. W., 52
Kirklin, J. W., 52, 394
Kistin, Albert D., 687
Klein, Michael D., 361
Kloster, Frank E., 415
Koler, Robert D., 570
Korns, Michael E., 589
Kossowsky, Warren A., 811
Krovetz, L. Jerome, 772
Krymsky, Leonard D., 814

Labrosse, Claude J., 708
LaMonte, Charles S., 746
Lane, Francis J., 361
Langendorf, R., 69, 386
Laragh, John H., 682
Latson, J. R., 293
Leachman, R. D., 65
Levin, Aaron R., 593
Levitt, M. F., 5
Levy, M., 130
Lewis, Kenneth B., 881
Liggett, M. S., 84
Lillehei, C. W., 258, 782
Linhart, Joseph W., 549
Linton, Robert R., 517
Littman, E., 5
Love, W. D., 309
Lowe, Harold M., 888
Luebs, E.-D., 636
Lugo, J. E., 251
Luisada, Aldo A., 563

MacCanon, Donald M., 563
McGill, Henry C., Jr., 948
McNamara, D. G., 293
Maher, Frank T., 394
Majd, M., 193
Manion, William C., 406
Maldague, Paul, 451
Mason, Dean T., 755
Mathur, B. B., 281
Mattingly, Thomas W., 845
Megahed, Gamal E., 925
Mehrizi, A., 35
Melnick, Gilbert S., 876
Meltzer, Jay I., 682
Méndez, J., 106
Meyers, A., 43
Mielke, John E., 394
Miller, R. A., 956, 966
Millikan, Clark H., 438
Milne, Walter S., 956
Ming, Si-Chun, 332
Morrow, A. G., 223, 608
Moser, Kenneth M., 377
Muller, Otto F., 477
Muster, A. J., 265

Nadas, A. S., 114, 172

Odendaal, W. A., 940
Okabe, N., 538

Palmero, H. A., 84
Page, I. H., 513
Paul, M. H., 265, 956, 966
Pearce, Morton Lee, 911
Perloff, J. K., 193, 204
Phillips, John H., 985
Pick, A., 69, 386
Plauth, W. H., Jr., 223
Porter, G. A., 169
Prado, S., 130
Preisig, Rudolph, 524
Pusch, A. L., 35

Read, Raymond C., 897
Reale, A., 214
Reeves, T. Joseph, 622
Resnekov, Leon, 797
Restivo, R. M., 956, 966
Ritzmann, Leonard W., 415
Roberts, William C., 342
Rogers, Terry R., 802
Roman, Laurian, 435
Ronan, J. A., Jr., 204
Ross, J. Jr., 549, 677
Ross, R. S., 630, 881
Rowe, G. G., 251

Sanders, C. A., 425, 597
Sanghvi, L. M., 281
Schamroth, L., 43
Scherlis, L., 134
Schmidt, R. E., 232, 241
Schrire, V., 721
Schwab, Robert H., 352
Seaward, P. D., 940
Segal, Jack P., 837
Sheffield, L. T. 622
Simmons, R. L., 258
Singelyn, Michael, 888
Singleton, R. T., 134
Sissman, Norman J., 582
Slodki, Sheldon J., 563
Smith, J. M., 956, 966
Somerville, Jane, 797
Sonnenblick, Edmund H., 677
Spach, Madison S., 593
Stamler, J., 956, 966
Stansell, G. B., 936
Starr, Albert, 570
Strong, Jack P., 948
Subramanian, S., 977
Sumner, Robert G., 985
Sutherland, Donald W., 570
Swan, H. J. C., 52

Taber, E., 32
Taylor, R. R., 778
Thal, Alan P., 897
Tucker, Donald H., 985
Tuhý, J., 992
Thurmann, M., 290
Thomson, Norman B., Jr., 732
Todd, D. B., 258, 298
Toole, James F., 346
Twigg, H., 193

Van Cleve, Robert, 878
Van der Hauwaert, Luke G., 451
van Lingen, B., 940
Varco, R. L., 130, 808
Varga, Zoltan, 636
Vogel, John H. K., 788

Walsh, J. J., 19, 852
Wannamaker, L. W., 1054
Waterston, D. J., 977
Wedeen, R. P., 5
Wendt, Vernon E., 897
Wheeler, Henry O., 524
White, P. D., 538
White, R. I. Jr., 881
Wigle, E. Douglas, 708
Williams, J. F. Jr., 608, 767
Wong, Peter C. Y., 425

Yamanaka, Jiro, 636
Yassin, Ahmed M., 925

Zaleski, Edward J., 636

Kelly, T. E., 32
Kennedy, J. H., 76
Killough, John H., 352
Kimsey, Jean A., 570
Kincaid, O. W., 52
Kirklin, J. W., 52, 394
Kistin, Albert D., 687
Klein, Michael D., 361
Kloster, Frank E., 415
Koler, Robert D., 570
Korns, Michael E., 589
Kossowsky, Warren A., 811
Krovetz, L. Jerome, 772
Krymsky, Leonard D., 814

Labrosse, Claude J., 708
LaMonte, Charles S., 746
Lane, Francis J., 361
Langendorf, R., 69, 386
Laragh, John H., 682
Latson, J. R., 293
Leachman, R. D., 65
Levin, Aaron R., 593
Levitt, M. F., 5
Levy, M., 130
Lewis, Kenneth B., 881
Liggett, M. S., 84
Lillehei, C. W., 258, 782
Linhart, Joseph W., 549
Linton, Robert R., 517
Littman, E., 5
Love, W. D., 309
Lowe, Harold M., 888
Luebs, E.-D., 636
Lugo, J. E., 251
Luisada, Aldo A., 563

MacCanon, Donald M., 563
McGill, Henry C., Jr., 948
McNamara, D. G., 293
Maher, Frank T., 394
Majd, M., 193
Manion, William C., 406
Maldague, Paul, 451
Mason, Dean T., 755
Mathur, B. B., 281
Mattingly, Thomas W., 845
Megahed, Gamal E., 925
Mehrizi, A., 35
Melnick, Gilbert S., 876
Meltzer, Jay I., 682
Méndez, J., 106
Meyers, A., 43
Mielke, John E., 394
Miller, R. A., 956, 966
Millikan, Clark H., 438
Milne, Walter S., 956
Ming, Si-Chun, 332
Morrow, A. G., 223, 608
Moser, Kenneth M., 377
Muller, Otto F., 477
Muster, A. J., 265

Nadas, A. S., 114, 172

Odendaal, W. A., 940
Okabe, N., 538

Palmero, H. A., 84
Page, I. H., 513
Paul, M. H., 265, 956, 966
Pearce, Morton Lee, 911
Perloff, J. K., 193, 204
Phillips, John H., 985
Pick, A., 69, 386
Plauth, W. H., Jr., 223
Porter, G. A., 169
Prado, S., 130
Preisig, Rudolph, 524
Pusch, A. L., 35

Read, Raymond C., 897
Reale, A., 214
Reeves, T. Joseph, 622
Resnekov, Leon, 797
Restivo, R. M., 956, 966
Ritzmann, Leonard W., 415
Roberts, William C., 342
Rogers, Terry R., 802
Roman, Laurian, 435
Ronan, J. A., Jr., 204
Ross, J. Jr., 549, 677
Ross, R. S., 630, 881
Rowe, G. G., 251

Sanders, C. A., 425, 597
Sanghvi, L. M., 281
Schamroth, L., 43
Scherlis, L., 134
Schmidt, R. E., 232, 241
Schrire, V., 721
Schwab, Robert H., 352
Seaward, P. D., 940
Segal, Jack P., 837
Sheffield, L. T. 622
Simmons, R. L., 258
Singelyn, Michael, 888
Singleton, R. T., 134
Sissman, Norman J., 582
Slodki, Sheldon J., 563
Smith, J. M., 956, 966
Somerville, Jane, 797
Sonnenblick, Edmund H., 677
Spach, Madison S., 593
Stamler, J., 956, 966
Stansell, G. B., 936
Starr, Albert, 570
Strong, Jack P., 948
Subramanian, S., 977
Sumner, Robert G., 985
Sutherland, Donald W., 570
Swan, H. J. C., 52

Taber, E., 32
Taylor, R. R., 778
Thal, Alan P., 897
Tucker, Donald H., 985
Tuhý, J., 992
Thurmann, M., 290
Thomson, Norman B., Jr., 732
Todd, D. B., 258, 298
Toole, James F., 346
Twigg, H., 193

Van Cleve, Robert, 878
Van der Hauwaert, Luke G., 451
van Lingen, B., 940
Varco, R. L., 130, 808
Varga, Zoltan, 636
Vogel, John H. K., 788

Walsh, J. J., 19, 852
Wannamaker, L. W., 1054
Waterston, D. J., 977
Wedeen, R. P., 5
Wendt, Vernon E., 897
Wheeler, Henry O., 524
White, P. D., 538
White, R. I. Jr., 881
Wigle, E. Douglas, 708
Williams, J. F. Jr., 608, 767
Wong, Peter C. Y., 425

Yamanaka, Jiro, 636
Yassin, Ahmed M., 925

Zaleski, Edward J., 636

CIRCULATION

VOLUME XXXII JULY-DECEMBER, 1965

SUBJECT INDEX

(Page numbers in *Italics* refer to abstracts)

A

Abdomen
aortic aneurysm with vena caval fistula, *663*
circulatory and acid-base changes during operation for aortic aneurysm, *494*
mesenteric arterial insufficiency and abdominal angina, *663*

Abscess
of myocardium *1046*

ACTH
10-year report on cortisone, aspirin and, in treatment of rheumatic fever and rheumatic heart disease, 451

Adams-Stokes disease. *See* Stokes-Adams disease

Adrenalectomy
for hypertension, *320*

Adrenaline
responses to, in cats during hypoxia, hyperventilation and hypoxia, *488*

Alcoholic heart disease, *1050*

Alkali
effect of glucose infusion and, on permanent brain damage in rhesus monkeys, *488*

Alpha-methyldopa
controlled study of, *319*

American Board of Internal Medicine
roster of Subspecialty Board of Cardiovascular Disease, 499

American Board of Pediatrics, Inc.
Diplomates of the Subspecialty Board of Pediatric Cardiology of, June 1965, 505

Americans
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106

Amyl nitrite
effect on arteriolar and venous tone in forearm, 755
use in hemodynamic assessment of aortic valvular and muscular subaortic stenosis, *661*

Anaerobic metabolism
during exercise, *1047*

Anastomoses
coronary arteries, 1026
systemic-pulmonary
combined ventricular hypertrophy, 265
vascular—sutures, staple or glue, *496*

Anatomy
anomalous pulmonary venous return, 406
congenital heart disease, 814
coronary arteries, 1020
measurement of myocardial blood flow, 630
muscular architecture of left ventricle, 301
total anomalous pulmonary venous connection, 150

Anemia
hemolytic
after aortic valve replacement, 570

Anesthesia
Clinical anesthesia, Anesthesia and the Circulation (Fabian, ed.) *1036*
effect of halothane on carotid sinus baroreceptor activity, *322*
effects of surgery under general, on the electrocardiogram in ischaemic heart disease and hypertension, *153*

Aneurysms
abdominal aortic
circulatory and acid-base changes during operations for, *494*
with vena caval fistula, *663*
annular subvalvular left ventricular, 43
dacron tubes to replace, 515
popliteal artery arteriosclerotic, 515
surgical management, 517
strokes and, 559
ventricular septal, 981

Angiitis
necrotizing, associated with embolization of cholesterol, 660

Angina pectoris
clinicophysiologic factors in development of, 143
diagnosis
electrocardiogram during exercise, 477
effect of propranolol (inderal), *154*
in angina of effort, *155*
effects of nitroglycerin, 767
exercise graded by heart rate in electrocardiographic testing for, 622
mesenteric arterial insufficiency and abdominal angina, *663*
pathophysiology of cardiac pain, 138
ST segment, *316*
testing for, 622

Angiocardiography
contrast media
cardiopulmonary response to, *494*
diagnosis of congenital cardiac defects in infancy, *862*
fibroma of right ventricle, 451
perforation after, 593
thrombosis of pulmonary arteries, 377

Angiography
renal, 682
strokes, 559

Angiotensin
measurement of, 513

Animals
cardiopulmonary response to injections of angiographic contrast medium, *494*

cats
responses to adrenaline and nor-adrenaline during hypoxia, hyperventilation and hypoxia, *488*
chickens
effects of Recosen on myocardial explants, *320*
dogs
architecture of left ventricle, 301
arrhythmias following condenser discharges led through an inductance, *659*
changes in coronary blood flow by central nervous stimulation, *492*
determination of coronary flow with a positron emitter, 636
direct and reflex effects of hypoxia, hypotension and hypothermia on heart, *322*
effects of pacemaker site on cardiac output and ventricular activation in dogs with complete heart block, *489*
effect on epinephrine on contractile tension and phosphorylase activation, *321*
electrocardiographic and vectorcardiographic changes produced by electrical stimulation of cardiac nerves, *492*
electrocardiographic effects of myocardial lesions, *1047*
experimental heart block, *657*
hemodynamic basis for clinical manifestations of patent ductus arteriosus, *151*
indicator dilution methods for determination of ventricular volume, *316*
intracardiac phonocardiography, 563
measuring myocardial blood flow, 630
pathogenesis of ventricular fibrillation, *660*
reduction of hyperbaric oxygenation of the mortality from ventricular fibrillation following coronary artery ligation, *656*
sodium and potassium citrate salts for treatment of digitalis toxicity, *320*
stenoses of arteries of lower extremity, *662*
effect of halothane on carotid sinus baroreceptor activity, *322*
mice
effects of Recosen on myocardial explants, *320*
monkeys
effect of alkali and glucose infusion on permanent brain damage in, asphyxiated at birth, *488*
effect of drugs and brain metabolism on internal carotid arterial flow, *489*
myocarditis in, 318
rabbits
effect of rhinencephalic lesions on cardiovascular reactions to nor-adrenaline, *490*
induction of arterial lipogenesis by red cells, *660*
pronethalol and oxygen consumption, *321*
rats
effect of epinephrine on contractile tension and phosphorylase activation, *321*
free nucleotides in myocardium of, under acute muscular stress, *492*
myocardial lipids after intense muscular work, *860*
neurogenic hypertension, *1051*
vascular anastomosis—sutures, staples or glue, *496*

Anticoagulants
Anticoagulant Therapy in Ischemic Heart Disease; An International Symposium (Nichold, ed.), *1034*
comparison of warfarin sodium and bishydroxycoumarin, *860*
coumarin, *860*
indanedione, *860*
primary myocardial disease, 843, 854, 857
therapy
myocardial infarction during long-term, *860*
rebound phenomenon after discontinuation of long-term, 878
See also Coagulants

Aorta
coarctation
supravalvular aortic stenosis, *149*
surgical one-stage correction of supravalvular aortic stenosis and, *495*
effects of myocardial hypothermia or coronary perfusion during aortic occlusion, 372
insufficiency. *See* Insufficiency, aorta
occlusion
studies of contractile force, 372
poststenotic dilation, muscular subaortic stenosis, *662*
stenosis. *See* Stenosis, aortic
See also Subaorta

Aortic arch
Ehlers-Danlos syndrome, 602
severe pulmonic stenosis with intact ventricular septum and, 114

Aortic regurgitation
immediate diastolic murmur, 797

Aortic Stenosis (Cullhed), 1034

Aortic valve
disease
blood flow, 251
red blood cell survival, 570
studies of contractile force, 372
myxomatous transformation, 897
nomogram for estimation of area, 425
replacement
hemolytic anemia following, 570
renal performance in patients undergoing, 394

Aortography
catheter
mechanical hazards, 876

Arcus senilis
in ischemic heart disease, *859*

Arrhythmias
auricular fibrillation in asymptomatic young man—effects of exercise, digitalization, atropinization, *657*
bloodless analysis of conduction disturbances in implanted electric pacemakers, *658*
cardiac output by external radioisotope counting in atrial fibrillation, *659*
complete heart block, *658*
concealed AV conduction, 386
diphenylhydantoin sodium in treatment of, *657*
disorder of rhythm appearing after implantation of synchronized pacemakers, *656*
disturbances of rate, rhythm and conduction in acute myocardial infarction, *657*
experimental heart block in dogs, *657*
following cardiac operations, 608
following condenser discharges led through an inductance, *659*
hemodynamic studies in patients with artificial pacemakers, *659*
myocardial infarction following electrocution, *658*
pacemaking on demand in AV block, *658*
paroxysmal ventricular tachycardia, 778
pathogenesis of ventricular fibrillation, *660*
primary myocardial disease, 842, 857

reduction by hyperbaric oxygenation of the mortality from ventricular fibrillation following coronary artery ligation, *656*
sodium diphenylhydantoin in treatment of recurrent, *656*
suppression of, by artificial pacemaking, *659*
supraventricular
use of diphenylhydantoin sodium, *657*
vagovagal syncope associated with diffuse esophageal spasm, *658*

Arterial Disease (Mitchell and Schwartz), 1034

Arteries
anastomoses, 1026
anatomy, 1020
AV node, 1025
forearm
effect of nitroglycerin and amyl nitrite on, 755
to interventricular septum, 1024
mesenteric
insufficiency, *663*
occlusive disease
hyperbaric oxygenation therapy, 936
to papillary muscles, 1023
reconstructive operation, 515
sinus node, 1025
stenoses of, of lower extremity, *662*
tissue
influence of unsaturated fat diet on, 911
See also Specific artery and/or condition

Arteriography
coronary, *493*

Arteriosclerosis
popliteal aneurysms, 517

Arteriovenous communications
abnormal, 1001

Arteriovenous fistulas
internal iliac artery and vein, *662*

Arteriovenous malformations
strokes and, 559

Ascites
use of triamterene, *862*

Aspirin
10-year report on use of ACTH, cortisone and, in treatment of rheumatic fever and rheumatic heart disease, 451

Atherogenesis
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106

Atheromata
influence of unsaturated fat diet on, 911

Atherosclerosis
arcus senilis in ischemic heart disease, *859*
calcification of carotid siphon, 538
coronary calcification, 948
effect of glucose on postprandial lipemia, *859*
effects of exercise on serum lipids, *859*
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106
focal cerebral ischemia, 438
induction of arterial lipogenesis by red cells, *660*
Metabolism of Lipids as Related to Atherosclerosis. A Symposium (Kummerow), *1040*
myocardial lipids after intense muscular work, *860*
necrotizing angiitis associated with embolization of cholesterol, *660*
paraostial, *154*
pediatrics and, *859*

Atresia
pulmonary
coronary artery-right ventricular fistula, 582
tricuspid
palliative surgery, 977

Atrioventricular block. *See* Heart block

Atrioventricular canal
persistent common, anatomy and function in relation to surgical repair, 120

Atrioventricular conduction system
behavior of left atrial pressure and simultaneously measured left ventricular diastolic pressure in mitral stenosis, *491*
controlling heart rate by means of electrical pacemaker, 549
disorders of rhythm appearing after implantation of synchronized pacemakers, *656*
experimental demonstration of concealed, 386

Atrioventricular defects
immediate diastolic murmur, 797

Atrioventricular fistula
due to penetrating wound of heart, 995

Atrioventricular (AV) junction
role of concealed conduction, 69

Atrioventricular valve
inverted malformations in corrected transposition of the great vessels, 298

Atrioventricularis communis
clinical aspects and surgical treatment, *151*

Atrium
fibrillation
acute effects of countershock conversion of, upon right and left heart hemodynamics, 214
cardiac output by external radioisotope counting, *659*
coarse, in congenital heart disease, 290
effects of exercise, digitalization, atropinization and restoration of normal rhythm, *657*
ventricular response in, 69
fibrillation or flutter
digitalized patients converted to sinus rhythm from, 58
reciprocal rhythm, 687
right
effects of changing heart rate by electrical stimulation of, 549
idiopathic enlargement, 985
pseudo P pulmonale, 96
septal defects
electrocardiogram and frontal vectorcardiogram in ostium secundum defect and endocardial cushion defect, *149*
immediate diastolic murmur, 797
Lutembacher syndrome, 589
systole
influence of contribution, to cardiac dynamics at a fixed ventricular rate, 84

Atropine
effects on auricular fibrillation in asymptomatic young man, *657*

Auscultation
effect of stethoscope-applied pressure, 430

B

Back
straight back syndrome, 193

Bacteremic shock
hypothermia in, *322*

Baroreceptor
renal control of acute renin release in normotensive, nephrogenic and neurogenic dogs, *1052*

Baroreceptor fibers
aortic threshold and sensitivity, *1050*

Beta-adrenergic blockade
for tachycardia, 778

Bethanidine
hypertension treated with, *319*

Biopsy
myocardial, *1050*
technique utilizing the ventricular septum, *663*

Birth
effect of alkali and glucose infusion on permanent brain damage in rhesus monkeys asphyxiated at, *488*

Bishydroxycoumarin
warfarin compared with, *860*

Block. *See* Bundle-branch block; Heart block

Blood
coagulation. *See* Coagulation
lipid-accumulating potential of whole, *660*
origin of, withdrawn from deep forearm veins during rhythmic exercise, *489*

Blood flow
in aortic valve disease, 251
cerebral
effect of drugs and brain metabolism on internal carotid arterial flow, *489*
coronary
changes in, *492*
coincidence counting system with rubidium-84, 636
demonstrated by cineangiocardiography, 582
isotope technics, 309
myocardial
measurement of, 630
quantitative determination, with positron emitter (Rubidium-84), 636
subclavian steal syndrome, 346

Blood pressure
behavior of left atrial pressure and simultaneously measured left ventricular diastolic pressure in patient with mitral stenosis, *491*
See also Pressure

Blood volume
effect of supine exercise on left ventricular volume and oxygen consumption, 361
isotope technics, 309
plasma volume after posture change in hypertensive subjects, *1051*
splanchnic, 524

Body water. *See* Water, body

Books
received, 1042
reviews, 1034

Bradycardia
role in retention of sodium and water in complete heart block, *862*

Brain
changes in coronary blood flow by central nervous stimulation, *492*
damage
effect of alkali and glucose infusion on permanent, in rhesus monkeys, *488*
metabolism
effect of drugs and, on internal carotid arterial flow, *489*

Bretylium tosylate
effect of guanethidine and, on essential hypertension, *320*

Bundle-branch block
congenital familial cardiac conduction defects, 32
disturbances of rate, rhythm and conduction in acute myocardial infarction, *657*
right
by diaphragmatic inspiration independent of heart rate, *317*
U vector loop, *317*
ST segment, *316*

Bypass
cardiopulmonary
aortic valve replacement, 394
atrioventricularis communis, *151*
late response to correction of pulmonary stenosis, 258
pulmonary artery banding, 172
saphenous vein, *662*

C

Calcification
of carotid siphon, 538
coronary, 948

Cardiac hypertrophy, 830
See also Primary myocardial disease

Cardiac output
effect of changing heart rate, 549
effect of smoking on stroke volume and, *491*
effects of isoproterenol infusion, 549
by external radioisotope counting in atrial fibrillation, *659*
low cardiac output syndrome, 612
patients with artificial pacemakers, *659*

Cardiomyopathy, 830
biochemical studies in familial, *318*
See also Primary myocardial disease

Cardiovascular system
hemorrhagic necrosis of the gastrointestinal tract and, 332

Carditis
diagnosis of rheumatic fever, 664
diagnostic test for
lactic dehydrogenase, 925
U.K. and U.S. joint report on rheumatic heart disease, 451

Carotid artery
calcification of siphon, 538
effects of drugs and brain metabolism on internal blood flow, *489*

Carotid sinus baroreceptor
effect of Halothane on, *322*

Catheter
impacted in coronary vein, 808
mechanical hazards in aortography, 876
positive torque-control (Positrol), 932

Catheterization
catheter impacted in coronary vein, 808
embolism after, 811
intracardiac phonocardiography, 563
krypton-85 in detecting intracardiac left-to-right shunts, 134
left heart
removal of foreign bodies, 782
transient changes of S-T and T in electrocardiogram, *1048*
transseptal, *156*
lodged catheter during, *317*
nomogram for estimation of cardiac valve areas, 425
valvular insufficiency during, *491*
ventricular septal defect and cardiac failure in infants, *150*

Central nervous system
complications after cardiac surgery, 614

Cerebral hemorrhage
in population after decade of antihypertensive treatment, *319*

Cerebrovascular disease
calcification of carotid siphon, 538
focal cerebral ischemia, 438
occlusive, diagnosis, 559

Chicago area high school study
detection of heart disease in children, 966

Childbirth
arteriovenous fistula of internal iliac artery and vein due to trauma at, *662*

Children
cardiac perforation after angiocardiography, 593
coronary artery–right ventricular fistula, 582
Ehlers-Danlos syndrome, 602
Fallot's tetralogy
relationship between polycythemia and surgical mortality, 65
heart disease detection
Chicago area high school study, 966
Michigan City study, 956
mitral insufficiency due to anomalous origin of left coronary artery from pulmonary artery, *150*
multiple muscular ventricular septal defects, 35
"parachute" mitral value
replacement of, 130
precordial movements over right ventricle, 232
children with pulmonary stenosis, 241
protein-losing enteropathy secondary to constrictive pericarditis, *318*
pulmonary artery banding, 172
severe pulmonic stenosis with intact ventricular septum and right aortic arch, 114
single coronary artery–right ventricular fistula, 293
supravalvular aortic stenosis, *149*

Chloroquine
electrocardiograms after, 281

Chlorthalidone
value of, plus reserpine in moderately severe and severe hypertension, 13

Cholesterol
essential fatty acids in serum lipids of male rural Guatemalans and urban North Americans, 106
induction of arterial lipogenesis by red cells, *660*
necrotizing angiitis associated with embolization of, *660*

Chordae tendineae
mitral insufficiency due to anomalous origin of left coronary artery from pulmonary artery, *150*

Chorea
diagnosis of rheumatic fever, 664

Cigarette smoking. *See* Smoking

Cineangiocardiography
blood flow demonstrated by, 582
coronary artery–right ventricular fistula, 582
left ventricular
cardiac perforation following, 593

Circulation
abnormal arteriovenous communications, 1001
cardiovascular effects of therapy in congenital hypothyroidism, *1052*
coronary
general scheme, 1027
isolation of, 630
measuring myocardial blood flow, 630
descending limb of Starling curve and failing heart, 871
effect of interval training on heart, metabolism and, in gymnasts, *488*
effect of smoking on stroke volume and cardiac output, *491*
Human Foetal and Neonatal Circulation (Lind, Stern and Wegelius), 1039
respiratory and, studies in myocardial infarction and cardiogenic shock, *154*
splanchnic
effect of digoxin in, 524
See also Blood flow

Cirrhosis of the liver
use of triamterene, *862*

Coagulation
comparison of warfarin and bishydroxycoumarin, *860*
patients receiving coumarin and indanedione anticoagulants, *860*
See also Anticoagulants

Coarctation
aorta
supravalvular aortic stenosis, *149*
surgical one-stage correction of supravalvular and, *495*

Coincidence counting method
with positron emitter, rubidium-84, 636

Computer analysis
electrocardiograms
using linear regression technique, *1049*

Concealed conduction, 386
role in atrioventricular (AV) junction, 69

Conduction system
atrial reciprocal rhythm, 687
congenital familial defects, 32
experimental demonstration of concealed AV conduction, 386

Congenital anomalies
annular subvalvular left ventricular aneurysms, 43
anomalous pulmonary venous return, 406
aortic insufficiency, 352
atrioventricularis communis, clinical aspects and surgical treatment, *151*
cardiac defects in infancy, *862*
conduction defects, 32
cor triatriatum, *152*
coronary artery
with fistula to right ventricle, 293
endocardial cushion defect
electrocardiogram and frontal vectorcardiogram, *149*
Friedreich's ataxia, *150*
mitral insufficiency due to anomalous origin of left coronary artery from pulmonary artery, *150*
multiple muscular ventricular septal defects, 35
neonatal period, *152*
operative treatment of heart lesions, *495*
ostium secundum defect
electrocardiogram and frontal vectorcardiogram, *149*
"parachute" mitral valve
successful replacement in children, 130
patent ductus arteriosus, *861*
hemodynamic basis for clinical manifestations, *151*
right ventricle
diagnosis and surgical correction of total obstruction, *151*
supravalvular aortic stenosis, *149*
total anomalous pulmonary venous connection, *150*
transposition of great vessels, 298, *862*
ventricular septal defect
and cardiac failure, *150*
in infancy, *861*
See also Congenital heart disease; and specific conditions

Congenital heart disease
aortic stenosis, 661
coarse atrial fibrillation, 290
in neonatal period, *152*
pathologic anatomy, 814
See also Congenital anomalies; and specific conditions

Congestive heart failure. *See* Heart failure, congestive

Contractility, myocardial, 372
descending limb of Starling curve and failing heart, 871
effect of epinephrine on, *321*

Contrast media
cardiac perforation following, 593
cardiopulmonary response to, *494*

Cor pulmonale
Le Coeur Pulmonaire Chronique (Tourniaire et al.), *1040*
thrombosis of pulmonary arteries, 377

Cor triatriatum
diagnostic surgical enigma, *152*
immediate diastolic murmur, 797

Coronary arteries
anatomy, 1020
anomalies, 293
arteriography, *493*
atrioventricular fistula and ventricular septal defect due to penetrating wound of heart, 995
blood flow
changes in, *492*
disease, 1027
advances in detection of, 620
calcification, 948
cigarette smoking and, *1045*
determination of blood flow with a positron emitter (Rubidium-84), 636
diagnosis
myocardial ischemia after exercise, *1045*
dicumarol prophylaxis, *863*
electrocardiogram during exercise, 477
exercise graded by heart rate in testing for angina pectoris, 62
external cardiac rupture in myocardial infarction, *1046*
heart muscle clearance in coronary sclerosis, *1046*
kinetocardiographic changes in ischemic heart disease, 650
measurements of myocardial blood flow, 630
myocardial ischemia after exercise, method for detecting potential, *1045*
recognition of, 620
ruptured papillary muscle, 597
left
mitral insufficiency due to anomalous origin of, from pulmonary artery, *150*
ligation
reduction by hyperbaric oxygenation of mortality from ventricular fibrillation following, *656*
reconstruction of two-coronary system with dacron graft, 293
right ventricular fistula, 582
single left, with fistula to right ventricle, 293

Coronary vein
cardiac catheter impacted in, 808

Cortisone
10-year report on use of ACTH, aspirin and, in treatment of rheumatic fever and rheumatic heart disease, 451

Coumarin
coagulation studies, *860*

Countershock
acute effects of countershock conversion of atrial fibrillation upon right and left heart hemodynamics, 214
digitalis intoxication after, 58

Cushion defect
endocardial
electrocardiogram and frontal vectorcardiogram, *149*
persistent common atrioventricular canal, anatomy and function, 120

D

Death. *See* Mortality

Diagnosis
angina pectoris, 622
electrocardiogram during exercise, 477
arterial reconstructive operation, 515
Clinical Examination. A Textbook of Physical Diagnosis, 1037
combined ventricular hypertrophy, 265
congenital cardiac defects, *862*
cor triatriatum, *152*
coronary artery disease
myocardial ischemia after exercise, *1045*
fibroma of right ventricle, 451
heart disease in children

Chicago area high school study, 966
Michigan City study, 952
tape-recorded sounds, 956
isoenzymes tests, 1010
necrotizing angiitis associated with embolization of cholesterol, with emphasis on use of muscle biopsy as aid in, *660*
precordial movements over right ventricle, 232
children with pulmonary stenosis, 241
primary myocardial disease, 831
rheumatic fever, 664
Jones criteria (revised) for, 664
right ventricle, total obstruction, *151*
serum enzyme tests, 1010
single left coronary artery with fistula to right ventricle, 293
standards for cardiac diagnostic and surgical centers, 497
strokes, 559
thrombosis of pulmonary arteries, 377
transposition of great vessels, *862*

Dicumarol prophylaxis
double-blind study of, in coronary heart disease, *863*

Diets
high unsaturated fat
influence on arterial tissue and atheromata, 911

Digitalis
effects on auricular fibrillation in asymptomatic young man, *657*
influence on contribution of atrial systole to cardiac dynamics at a fixed ventricular rate, 84
intoxication
after conversion to sinus rhythm, 58
primary myocardial disease, 842
toxicity
diphenylhydantoin sodium in cardiac arrhythmias, *657*
sodium and potassium citrate salts for, *320*

Digoxin
effect in splanchnic circulation, 524

Dilated heart
prolonged bed rest for, 852, 857

Dilation
descending limb of Starling curve and failing heart, 871

Diphenylhydantoin sodium
in treatment of arrhythmias, *656*, *657*

Diplomates
Subspecialty Board of Pediatric Cardiology of the American Board of Pediatrics, Inc., June, 1965, 505

Diuretics
Frusemide or Lasix, *863*
Fursemide or Lasix, *152*
primary myocardial disease, 854
triamterene, *862*, *863*
value of chlorthalidone plus reserpine in moderately severe and severe hypertension, 13

Drugs
effect of, and brain metabolism on internal carotid arterial flow, *489*
See also Specific drug and specific type

Ductus arteriosus
immediate diastolic murmur, 797
patent, *861*
hemodynamic basis for clinical manifestations of, *151*

Dye, indicator
dispersal of slugs, in tube with laminar flow, *317*
formulas for dispersal of slugs, *318*

Dye dilution
and cold injection methods, *1048*

E

Edema
body water and electrolyte composition in cardiac failure, 169
exchangeable sodium, body potassium and body water in previously edematous patients, 185
oral sodium tolerance test, 223

Ehlers-Danlos syndrome
cardiovascular aspects of, 602

Electrical stimulation
cardiac nerves, *492*
of right atrium
effects of changing heart rate, 549

Electricity
myocardial infarction following electrocution, *658*

Electrocardiograms
changes produced by electrical stimulation of cardiac nerves, *492*
after chloroquine and emetine, 281
coarse atrial fibrillation, 290
computer analysis
using linear regression technique, *1049*
concealed AV conduction, 386
disturbances of rate, rhythm and conduction in acute myocardial infarction, *657*
dye dilution and cold injection method, *1048*
effects of surgery under general anesthesia on, in ischaemic heart disease and hypertension, *153*
evaluation of multipolar effects, 273
exercise
for diagnosing angina pectoris, 477, 622
graded by heart rate, 622
significance of QX/QT ratio and the QT ratio (QTr), 435
experimental myocardial lesions, *1047*
factor analysis, 273
fetal, *1049*
horizontal plane electrocardiographic vectors, *1050*
after mastectomy, 746
monitored and post-exercise two-step tests, *155*
mumps of the heart, 342
muscular subaortic stenosis due to ventricular septal hypertrophy, *156*
nature of normal and abnormal, *1049*
ostium secundum defect and endocardial cushion defect, *149*
P wave
pseudo P pulmonale, 96
in quinine poisoning, *321*
ST segment, *316*, *1048*
straight back syndrome, 193
total anomalous pulmonary venous connection, *150*
transient changes of S-T and T during left cardiac catheterization, *1048*
ventricular premature beats in diagnosis of septal infarction, *1048*
ventricular response in atrial fibrillation, 69

Electrolyte disturbances
after cardiac surgery, 613

Electrolytes
body water and, in cardiac failure, 169

Embolism
atheromatous, *660*
after catheterization, 811
isotope technics, 309
necrotizing angiitis associated with embolization of cholesterol, *660*
systemic
patients with mitral stenosis and, *661*

Emetine
electrocardiograms after, 281

Emphysema, pulmonary
coarse atrial fibrillation, 290

Endocarditis
Lutembacher syndrome and, 589
mycotic vegetative, 589

Endocardium
studies on human mural, *1053*
See also Cushion defects, endocardial

Enterocolitis
acute hemorrhagic, 329

Enzymes
cardiac metabolism in early rat hypertension, enzyme histochemistry in prenecrotic phase, *1052*
isoenzymes in clinical diagnosis, 1010
selected list of mammalian, with multiple molecular forms, 1015
serum
in myocardial infarction, *1046*

Epinephrine
effect on contractile tension and phosphorylase activation, *321*

Erthrocytic phospholipid linoleic acid
in ischemic heart disease, *860*

Erythema marginatum
diagnosis of rheumatic fever, 664

Esophagus
vogovagal syncope associated with diffuse esophageal spasm, *658*

Exercise
anaerobic metabolism during, *1047*
blood flow in aortic valve disease, 251
effect of interval training on heart, circulation and metabolism in gymnasts, *488*
effect on auricular fibrillation, *657*
effect on heart rate, 549
effect on serum lipids, *859*
electrocardiograms
diagnosis of angina pectoris, 477
significance of the QX/QT ratio and the QT ratio (QTr), 435
graded by heart rate in electrocardiographic testing for angina pectoris, 622
origin of blood withdrawn from deep forearm veins during rhythmic, *489*
supine
effect on left ventricular volume and oxygen consumption, 361
work speed as measure of stress, in subjects of different weights, 940

Extremities
advanced ischemia, *662*
lower
stenoses of arteries, *662*
upper
hemodynamics of, in subclavian steal syndrome, 346

F

Factor analysis
of electrocardiograms, 273

Fallot's tetralogy
combined ventricular hypertrophy, 265
corrective surgery, *495*
severe pulmonic stenosis with intact ventricular septum and right aortic arch, 114
total correction
relationship between polycythemia and surgical mortality, 65

Familial incidence
biochemical studies in cardiomyopathy, *318*
conduction defects, 32
postpartal heart disease, 19

Fats
unsaturated
influence on arterial tissue and atheromata, 911

Fatty acid
erthrocytic phospholipid linoleic acid in ischemic heart disease, *860*
essential
in serum lipids of young male rural Guatemalans and urban North Americans, 106

Fetus
electrocardiography, *1049*
heart sounds, *316*
detection of fetal distress by radioelectrocardiogram, *317*

Fibre optics
spectrophotometer for in vivo oximetry, *1048*

Fibrillation
atrial. *See* Atrium, fibrillation
auricular
effects of exercise, digitalization and atropinization and restoration of normal rhythm, 657
ventricular
arrhythmias following condenser discharges led through an inductance, 659
pathogenesis of, *660*

Fibroelastosis
subendocardial, *318*

Fibroma
of right ventricle producing severe tricuspid stenosis, 451

Fistula
arteriovenous
abnormal arteriovenous communications, 1001
internal iliac artery and vein, related to trauma at childbirth, *662*
atrioventricular-coronary artery and ventricular septal defect due to penetrating wound of heart, 995
coronary artery–right ventricular, 582
right ventricle
single left coronary artery with, 293
vena cava
abdominal aortic aneurysm with, *663*

Floppy valve syndrome, 897

Flowmeter probes, 630

Forearm
effect of nitroglycerin and amyl nitrite on arteriolar and venous tone, 755

Foreign bodies
catheter impacted in coronary vein, 808
removal of iatrogenic, within cardiac chambers and great vessels, 782

Friedreich's ataxia
pathology, *150*

Frusemide (Lasix)
diuretic response to, *863*

Fursemide (Lasix)
diuretic response to, *152*

G

Gas liquid chromatographs
Steroid Analysis by Gas Liquid Chromatographs (Patti and Stein), *1040*

Gastrointestinal tract
hemorrhagic necrosis, 329
relation to cardiovascular status, 332

Glucose
effect on postprandial lipemia in ischemic heart disease, *859*

Glycogenosis
biochemical studies in familial cardiomyopathy, *318*
siblings with, 318
Gout (Talbott), *1038*

Grafts
autogenous saphenous vein, 515, 517
fate of dacron vascular, *495*
omental
myocardial revascularization by, *1047*
vascular
calcification in, in operated aortic isthmic stenosis, *494*

Great vessels
origin of both, from right ventricle with trisomy-18 syndrome, 802
See also Transposition of great vessels

Guanethidine
effect on essential hypertension of bretylium tosylate and, *320*
relationship between polyarteritis and, *319*

Guatemala
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106

H

Halothane
effect on carotid sinus baroreceptor activity, *322*

Heart
concealed AV conduction, 386
dilated, prolonged bed rest in treatment of, 852
effect of interval training on circulation and metabolism in gymnasts, *488*
left
transseptal catheterization, *156*
mumps, 342
paired electrical stimulation, 677
"pancake," straight back syndrome, 193
penetrating wound
coronary artery-atrioventricular fistula and ventricular septal defect due to, 995
rate. *See* Heart rate
removal of iatrogenic foreign bodies, 782
rupture
external, in myocardial infarction, *1046*
sounds. *See* Sounds, heart

Heart block
complete, *658*
role of bradycardia in retention of sodium and water in, *862*
concealed AV conduction, 386
congenital familial cardiac conduction defects, 32
effect of alterations in ventricular rate on cardiac output in, *490*
effect of pacemaker site on cardiac output and ventricular activation in dogs with complete, *489*
experimental, in dogs, *657*
influence of digitalization on contribution of atrial systole at a fixed ventricular rate, 84
pacemaking on demand in AV block, *658*

Heart disease
alcoholic, *1050*
congenital. *See* Congenital heart disease
coronary
ability to return to work after cardiac infarction, *155*
circulatory and respiratory studies in myocardial infarction and cardiogenic shock, *154*
effect of propranolol (inderal) in angina of effort, *155*
effect of propranolol (inderal) in angina pectoris, *154*
effects of surgery on the electrocardiogram in ischaemic heart disease and hypertension, *13*
elderly men in Scotland, *153*
hydrocortisone in severe myocardial infarction, *155*
incidence of coronary thrombosis in myocardial infarction, *153*
monitored and post-exercise two-step test, *155*
myocardial infarction, return to work of patients, *152*
papillary muscle rupture in myocardial infarction, *153*
paraostial atherosclerosis, *154*
surgical patients with, *152*
detection in children
Chicago area high school study, 966
Michigan City study, 956
hemorrhagic necrosis and, 332
ischemic
arcus senilis, *859*
effect of glucose utilisation on postprandial lipemia, *859*
effects of surgery on electrocardiogram, 153
erthrocytic phospholipid linoleic acid, *860*
kinetocardiographic changes in, 650
measuring myocardial blood flow, 630
postpartal
idiopathic myocardiopathy of the puerperium, 19
"pseudo," straight back syndrome, 193

rheumatic. *See* Rheumatic heart disease
valvular
congenital aortic stenosis, *661*
patients with mitral stenosis and systemic emboli, *661*
poststenotic dilation of the aorta with muscular subaortic stenosis, *662*
preoperative assessment of multiple valve disease, *661*
serious mitral stenosis with slight symptoms, *660*
use of amyl nitrite in hemodynamic assessment of aortic valvular and muscular subaortic stenosis, *661*

Heart failure
abnormal arteriovenous communications, 1001
body water and electrolyte composition, 169
congestive
diuretic response to Frusemide (Lasix), *863*
diuretic response to Fursemide (Lasix), *152*
diuretic triamterene for cirrhosis and ascites, *862*
effect of digoxin in splanchnic circulation, 524
exchangeable sodium, body potassium, and body water in previously edematous patients, 185
mitral insufficiency due to anomalous origin of left coronary artery from pulmonary artery, *150*
mumps of the heart, 342
oral sodium tolerance test, 223
pulmonary artery banding, 172
role of bradycardia in retention of sodium and water in complete heart block, *862*
treatment
with triamterene, *863*
descending limb of Starling curve and, 871
influence of digitalization on contribution of atrial systole at a fixed ventricular rate, 84
ventricular septal defect and, in infants, *150*

Heart rate
disturbances of rate, rhythm and conduction in acute myocardial infarction, *657*
effects of changing, by electrical stimulation, 549
exercises graded by, in testing for angina pectoris, 622
right bundle branch block by diaphragmatic inspiration independent of, *317*
studies at rest, during exercise, and with isoproterenol, 549
work speed as measure of exercise stress in subjects of different weights, 940

Hemodilution
aortic valve replacement, 394

Hemodynamics
acute effects of countershock, 214
aortic insufficiency, 708
basis for clinical manifestations of patent ductus arteriosus, 151
effects of digoxin in splanchnic circulation, 524
following pericardiectomy for constrictive pericarditis, 415
hypertension
effect of guanethidine and bretylium tosylate on systemic and renal, *320*
late response to correction of pulmonary stenosis, 258
mitral valve replacement, 721
renal
aortic valve replacement, 394
straight back syndrome, 193
studies in patients with artificial pacemakers, *659*
total anomalous pulmonary venous connection, *150*
upper extremities in subclavian steal syndrome, 346

Hemolysis, 617

Hemorrhage
gastrointestinal tract, necrosis, 329
Hemorrhage and Thrombosis. A Practical Clinical Guide (Salzman and Britten, ed.), *1039*

Hemorrhagic necrosis
of the gastrointestinal tract, 329
relation to cardiovascular status, 332

Hepatic amebiasis
use of chloroquine and emetine, 281

High altitudes
right ventricular hypertrophy in people born and living at, *1053*

Histoplasma capsulatum
cause of vegetative endocarditis, 589

Hospitals
Coronary Patient, Hospital Care and Rehabilitation (Nite and Willis), *1037*
standards for cardiac diagnostic and surgical centers, 497

Hydrochlorothiazide
controlled study of, *319*

Hydrocortisone
in severe myocardial infarction, *155*

Hydrogen ion concentration
role of regulation of pulmonary arterial pressure, 788

Hyperbaric chambers, *663*

Hyperbaric oxygenation
limitations of, in occlusive arterial disease, 936
reduction of mortality from ventricular fibrillation following coronary artery ligation, *656*

Hyperkalemia, 613

Hypertension
antihypertensive agents
alpha-methyldopa, *319*
hydrochlorothiazide, *319*
aortic baroreceptor threshold and sensitivity in rabbits, *1050*
assay of renin in single glomeruli in normal rabbit, *1051*
cardiac metabolism, enzyme histochemistry in prenecrotic phase, *1052*
cerebral hemorrhage in population after decade of antihypertensive treatment, *319*
detection of disparate kidney function
use of I^{131}-Hippuran renogram, 5
effect of guanethidine and bretylium tosylate on renal hemodynamics, 320
effects of hydrochlorothiazide and alpha-methyldopa, *319*
effects of surgery under general anesthesia on the electrocardiogram, *153*
following cardiac surgery, 618
guanethidine therapy, *320*
three cases resembling polyarteritis nodosa during, *319*
hypokalemia and, *1051*
after kidney injuries, 992
magnesium metabolism in, *1052*
neurogenic, in rats, *1051*
plasma volume after posture change, *1051*
polyarteritis nodosa after treatment with guanethidine, *319*

pulmonary
"primary" and Raynaud's phenomenon, *491*
surgical treatment of ventricular septal defect associated with, *495*
thrombosis of pulmonary arteries, 377
pulmonary artery banding, 172
renal baroreceptor control of acute renin release in normotensive, nephrogenic and neurogenic dogs, *1052*
renal disease, 682
salt loading, 888
renovascular
assessment of curable, by radiographic technics, *318*
due to renal ischemia, 1
use of I^{131}-Hippuran Renogram in detection of disparate kidney function, 5
retinal disease
Hypertensive Retinal Disease (Shelburne), *1040*
ST segment, *316*
surgery for
adrenalectomy and sympathectomy, *320*
treatment
bethanidine, *319*
propranolol (inderal), *320*
value of chlorthalidone plus reserpine, 13

Hypertrophic subaortic stenosis
pressure gradients without obstruction, 881

Hypertrophy
cardiac, 830
See also Primary myocardial disease,
myocardial
oral sodium tolerance test, 223
right atrial
total anomalous pulmonary venous connection, *150*
right ventricular
in people born and living at high altitudes, *1053*
precordial movements over right ventricle in children with pulmonary stenosis, 241
U vector loop, *317*
ventricular
combined, 265
ventricular septal
electrocardiogram in muscular subaortic stenosis due to, *156*

Hyperventilation
responses to adrenaline and nor-adrenaline in cats during hypoxia and, *488*

Hypokalemia, 613
and hypertension, 1051

Hyponatremia, 614

Hypotension
direct and reflex effects on heart, *322*

Hypothermia
in bacteremic shock, *322*
direct and reflex effects on heart, *322*
myocardial
effects during aortic occlusion, 372

Hypothyroidism
congenital
cardiovascular effects of therapy in, *1052*

Hypovascularization
idiopathic unilateral increased pulmonary luminosity with, *492*

Hypoventilation
role of hydrogen ion concentration in regulation of pulmonary arterial pressure, 788

Hypoxia
direct and reflex effects on heart, *322*
responses to adrenaline and nor-adrenaline in cats during, *488*

I

Idiopathic myocardial disease, 19
Idiopathic myocardial hypertrophy, 830
See also Primary myocardial disease

Iliac artery
arteriovenous fistula of internal, and vein, *662*
stenoses of arteries of lower extremity, *662*

Indicator dilution methods
determination of ventricular volume, *316*
effect of alterations in ventricular rate on cardiac output in complete heart block, *490*
for estimation of left-to-right shunts in infants, 772
spread to appearance time ratio in estimation of left-to-right shunts, *490*

Infants
congenital cardiac defects, *862*
congenital heart disease, *152*
Human Foetal and Neonatal Circulation (Lind, Stearn and Wegelius), *1039*
left-to-right shunts
use of indicator-dilution technics for estimating, 772
pulmonary artery banding, 172
severe pulmonic stenosis with intact ventricular septum and right aortic arch, 114
total anomalous pulmonary venous connection, *150*
ventricular septal defect, *861*

Infarction
myocardial. *See* Myocardial infarction
septal
diagnosis, *1048*

Instrumentation
isotope technics, 309

Insufficiency
aorta, 708
blood flow in aortic valve disease, 251
phonocardiographic differentiation of pulmonic and, 352
sudden severe, 708
cerebral vascular
subclavian steal syndrome, 346
coarse atrial fibrillation, 290
coronary
exercise electrocardiograms, 435
mesenteric artery, *663*
mitral valve
due to anomalous origin of the left coronary artery from the pulmonary artery, *150*
phonocardiographic differentiation of pulmonic and aortic, 352
valvular
during cardiac catheterization, *491*
myxomatous transformation, 897
ventricular
effect of digoxin in splanchnic circulation, 524

Interventricular septum
multiple muscular defects, 35

Ischemia
advanced, *662*

cerebral
observation of, *662*
pathogenesis of transient focal, 438
subclavian steal syndrome, 346
myocardial
effect of nitroglycerin on left ventricular wall tension in fixed orifice aortic stenosis, 204
after exercise, to detect coronary heart disease, *1045*
monitored and post-exercise two-step test, *155*
pathophysiology of pain, 138
renal
renovascular hypertension due to, 1

Isoenzymes
in clinical diagnosis, 1010

Isoproterenol
effect on heart rate, 549

Isotopes
techniques, 309
See also Radioisotopes

K

Kidneys
renin distribution, *1051*
renovascular hypertension due to renal ischemia, 1
rupture
hypertension after, 992
use of I^{131}-Hippuran Renogram in detection of disparate kidney function in hypertensive patients, 5

Kinetocardiograms
changes in ischemic heart disease, 650

Krypton-85
in detecting intracardiac left-to-right shunts, 134

Kyphosis, thoracic
straight back syndrome, 193

L

Lactic dehydrogenase
serum level as a diagnostic test for carditis in rheumatic fever, 925

Lasix
effective diuretic, *152, 863*

Lesions
atheromatous
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106
atherosclerotic
coronary calcification, 948
fibroma of right ventricle producing severe tricuspid stenosis, 451
hemorrhagic necrosis of the gastrointestinal tract, 329
myocardial
electrocardiographic effects, *1047*
operative treatment for congenital heart, *495*
rhinencephalic
effect on cardiovascular reactions to noradrenaline, *490*
subclavian steal syndrome, 346

Linoleic acid
in ischemic heart disease, *860*

Linolenic acid
prevention of thrombosis and myocardial infarction, *861*

Lipids
induction of arterial lipogenesis by red cells, *660*
Metabolism of Lipids as Related to Atherosclerosis. A Symposium (Kummerow), *1040*
myocardial
after intense muscular work, *860*
serum
effects of exercise on, *859*
essential fatty acids in, of young male rural Guatemalans and urban North Americans, 106

Liver
cirrhosis of
use of triamterene, *862*

Lutembacher syndrome
and endocarditis, 589

M

Magnesium metabolism
in hypertension, *1052*

Malformations
inverted
corrected transposition of great vessels, 298
See also Congenital anomalies

Marfan syndrome
possible forme fruste of, 897

Mastectomy
electrocardiogram after, 746

Mathematics
nomogram for estimation of cardiac valve areas, 425

Menghini needle, *663*

Metabolism
effect of interval training on heart, circulation and, in gymnasts, *488*
magnesium, in hypertension, *1052*

Methyldopa
antihypertensive agent, *319*

Michigan City study
detection of heart disease in children, 956

Microscopy
electron
ultra-structure of human cardiac muscle, *321*

Mitral valve
coarse atrial fibrillation, 290
disease
acute effects of countershock conversion of atrial fibrillation upon right and left heart hemodynamics, 214
insufficiency. *See* Insufficiency, mitral valve
nomogram for estimation of area, 425
replacement
left ventricular function after resection of the papillary muscles, *494*
"parachute" mitral valve in children, 130
results, *494*

ruptured papillary muscle with, 597
University of Cape Town prothesis, 721
stenosis. *See* Stenosis, mitral valve
surgery
persistent common atrioventricular canal, anatomy and function in relation to, 120
replacement of "parachute deformity" in children, 130

Mortality
congenital heart disease in neonatal period, *152*
incidence and management of "medical" complications following cardiac operations, 608
reduction by hyperbaric oxygenation of, from ventricular fibrillation following coronary artery ligation, *656*
relationship between polycythemia and, in patients undergoing total correction for tetralogy of Fallot, 65
surgical patients with coronary artery disease, *152*

Mumps
of the heart, 342

Murmurs
Graham Steell, 352
immediate diastolic
in atrioventricular defects, 797
new portable heart sound recording system, *156*
phonocardiographic differentiation in pulmonic and aortic insufficiency, 352
straight back syndrome, 193

Muscles
architecture of left ventricle, 301
biopsy, 660
clearance in coronary sclerosis, *1046*
multiple muscular ventricular septal defects, 35
ultra-structure of human cardiac, on basis of electron microscopy, *321*
See also Papillary muscles

Myocardial infarction
ability of men to return to work after, *152, 155*
abnormal recordial pulsation, 650
abscess of myocardium, *1046*
acute
denial of pain, *1046*
disturbances of rate, rhythm and conduction, 657
use of hydrocortisone, *155*
anticoagulation therapy, *860*
rebound phenomenon after discontinuation of long-term, 878
circulatory and respiratory studies, *154*
diagnosis
premature beats, *1048*
during long-term anticoagulant therapy, *860*
external cardiac rupture, *1046*
following electrocution, 658
incidence of coronary thrombosis, 153
kinetocardiographic changes in ischemic heart disease, 650
linolenic acid for prevention of, *861*
papillary muscle rupture in, *153*, 597
postinfarction ventricular septal defect, 76
serum enzymes, *1046*
U vector loop, *317*

Myocardiopathy, 830
See also Primary myocardial disease

Myocarditis
in rhesus monkeys, *318*

Myocardium
abscess of, *1046*
architecture of left ventricle, 301
biopsy, *1050*
new technique utilizing the ventricular septum, *663*
blood flow
coincidence counting system with rubidium-84, 636
measurement of, 630
contractile force. *See* Contractility, myocardial
effects of emetine, 281
effects of myocardial hypothermia during aortic occlusion, 372
explants
effects of Recosen on rhythmical contraction of, *320*
free nucleotides in, of rats undergoing intense muscular activity, *492*
hypertrophy
idiopathic, 830
oral sodium tolerance tests, 223
See also Primary myocardial disease
idiopathic myocardiopathy of the puerperium, 19
infarction. *See* Myocardial infarction
ischemia
effect of nitroglycerin on left ventricular wall tension in fixed orifice aortic stenosis, 204
after exercise, to detect coronary heart disease, *1045*
monitored and post-exercise two-step test, *155*
pathophysiology of pain, 138
lesions
electrocardiographic effects of experimental, *1047*
lipids
after muscular work, *860*
mumps of the heart, 342
oxidative metabolism
blood flow in aortic valve disease, 251
oxygen requirements
effect of nitroglycerin on left ventricular wall tension in fixed orifice aortic stenosis, 204
primary myocardial disease. *See* Primary myocardial disease
revascularization by omental graft without pedicle, *1047*

Myocardosis, 830
See also Primary myocardial disease

Myxomatous transformation
aortic and mitral valves, 897

N

Negroes
annular subvalvular left ventricular aneurysms, 43
idiopathic myocardiopathy of the puerperium (postpartal heart disease), 19

Nerves, cardiac
electrocardiographic and vectorcardiographic changes produced by electrical stimulation of, *492*

Nervous system
central
complications after cardiac surgery, 614

Neuroblastoma
diagnosis of pheochromocytoma and, *492*

Nitroglycerin
effects of, 767
on arteriolar and venous tone in forearm, 755

on left ventricular wall tension in fixed orifice aortic stenosis, 204

Nodules
subcutaneous
diagnosis of rheumatic fever, 664

Nomograms
for estimation of cardiac valve areas, 425

Noradrenaline
effect of rhinencephalic lesions on cardiovascular reactions to, *490*
response to, in cats during hypoxia, hyperventilation and hypoxia, *488*

Nucleotides
in myocardium of rats under intense muscular stress, *492*

O

Obesity, chronic
cardiac pathology, 740
role of hydrogen ion concentration in regulation of pulmonary arterial pressure, 788

Obstruction
pressure gradients without
hypertrophic subaortic stenosis, 881

Occlusion
aortic
effects of myocardial hypothermia or coronary perfusion during, 372
arterial
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106
coronary
topography of, 1028
focal cerebral ischemia, 438
thromboendartectomy for chronic, massive, 384

Occlusive arterial disease
hyperbaric oxygenation in, 936

Occlusive vascular disease
Biological Aspects of Occlusive Vascular Disease (Chalmers and Gresham, ed.), 1035

Omental graft
without pedicle
myocardial revascularization by, *1047*

Ostium secundum defect. *See* Cushion defect

Output, cardiac. *See* Cardiac output

Oxygen
consumption
effect of supine exercise on left ventricular volume and, 361
pronethalol and, of new-born rabbits, *321*
reduction by hyperbaric oxygenation of the mortality from ventricular fibrillation following coronary artery ligation, *656*
requirements
effect of nitroglycerin on left ventricular wall tension
saturation
krypton-85 in detection of intracardiac left-to-right shunts, 134
See also Hyperbaric oxygenation

P

P wave
pseudo P pulmonale, 96

Pacemakers, cardiac
bloodless analysis of conduction disturbances in implanted electric, *658*
changing heart rate, 549
concealed AV conduction, 387
on demand in AV block, *658*
disorders of rhythm appearing after implantation of synchronized, *656*
effect of site, on cardiac output and ventricular activation in dogs with complete heart block, *489*
Elema-Schönander, *658*
hemodynamic studies in patients with artificial, *659*
implanted because of complete heart block, *658*
Medtronic, *658*
suppression of arrhythmias by artificial, *659*

Pain, cardiac
denial of, in acute myocardial infarction, *1046*
effect of nitroglycerin on left ventricular wall tension in fixed orifice aortic stenosis, 204
pathophysiology of, 138

Paired electrical stimulation of the heart, 677

Palpation
precordial movements over right ventricle
children with pulmonary stenosis, 241
in normal children, 232

Papillary muscles
resection of, *494*
ruptured, 597
in myocardial infarction, *153*

Paraostial atherosclerosis, *154*

Patent ductus arteriosus; *See under* Ductus arteriosus

Pathology
carotid siphon calcification, 538
chronic obesity, 740
congenital heart disease, 814
focal cerebral ischemia, 438
Friedreich's ataxia, *150*
hemorrhagic necrosis of the gastrointestinal tract, 332
human mural endocardium, *1053*
mumps of the heart, 342
primary myocardial disease, 831
right ventricular hypertrophy in people born and living at high altitudes, *1053*
strokes, 559

Pathophysiology
cardiac pain, 138

Patients, coronary
Coronary Patient. Hospital Care and Rehabilitation (Nite and Willis), *1037*

Pediatrics
atherosclerosis and, 859
diplomates of the Subspecialty Board of Pediatric Cardiology of the American Board of Pediatrics, Inc., June, 1965, 505
Essentials of Paediatric Cardiology (Venables), *1037*

Perforation, cardiac
following left ventricular cineangiocardiography, 593

Perfusion
bilateral, 372
coronary
effects of myocardial hypothermia or, during aortic occlusion, 372

Pericarditis
acute constrictive, *1050*
hemodynamic studies following pericardiectomy for constrictive, 415
protein-losing enteropathy secondary to constrictive, *318*

Pharmacology
effects of Recosen on myocardial explants, *320*
epinephrine
effect on contractile tension and phosphorylase activation, *321*
pronethalol
and oxygen consumption of new-born rabbits, *321*
quinine
electrocardiogram in poisoning, *321*
sodium and potassium citrate salts for treatment of digitalis toxicity, 320

Pheochromocytoma
diagnosis of neuroblastoma and, *492*

Phonocardiography
Clinical Phonocardiography (Duchar), *1037*
differentiation of pulmonic and aortic insufficiency, 352
fibroma of right ventricle, 451
fluid column transmission method, 563
intracardiac, 563
precordial movements over right ventricle
children with pulmonary stenosis, 241
in normal children, 232
straight back syndrome, 193

Phosphorylase activation
effect of epinephrine on, *321*

Physiology
direct and reflex effects of hypoxia, hypotension and hypothermia, *322*
effect of halothane on carotid sinus baroreceptor activity, *322*
measurement of myocardial blood flow, 630
ultra-structure of human cardiac muscle on basis of electron microscopy, *321*

Plaques
fibrous
essential fatty acids in serum lipids of young male rural Guatemalans and urban North Americans, 106

Plasma
volume
after posture change, in hypertensive subjects, *1051*

Polyarthritis
diagnosis of rheumatic fever, 664

Polyarteritis nodosa, *660*
after treatment with guanethidine, *319*

Polycythemia
relationship between surgical mortality and, in patients undergoing total correction for tetralogy of Fallot, 65

Pompe's disease. *See* Glycogenosis

Popliteal aneurysms
prosthetic replacement, 517
surgical management, 517

Popliteal artery
arteriosclerotic aneurysm, 515

Positron emitter (Rubidium-84)
for determining blood flow, 636

Postextrasystolic potentiation, 677

Postpartal heart disease
idiopathic myocardiopathy of the puerperium, 19

Postprandial lipemia
in ischemic heart disease, *859*

Potassium
body water and electrolyte composition in cardiac failure, 169
exchangeable sodium, body water, and potassium in previously edematous patients, 185
primary myocardial disease, 854
use after chloroquine and emetine therapy, 281

P-pulmonale pattern, 96

Precordial pulsations
kinetocardiographic changes in ischemic heart disease, 650
over right ventricle
in children with pulmonary stenosis, 241
in normal children, 232

Pregnancy
serious mitral stenosis with slight symptoms, *660*

President's Commission on Heart Disease, Cancer, and Stroke, 686

Pressor agents
angiotensin, 513

Pressure
arterial
use of amyl nitrite in assessment of aortic valvular and muscular subaortic stenosis, *661*
gradients
hypertrophic subaortic stenosis, 881
pulmonary artery
role of hydrogen ion concentration, 788
See also Blood pressure

Primary myocardial disease, *828*
clinical recognition, 828, 835, 837, 846
coronary artery disease, 834
definition and classification, 830, 845
diagnosis, 831
electrocardiogram, 840
etiology, 830
hypertension, 833
management, 847
pathologic data, 831
pericardial disease, 832
prognosis and prevention, 851, 854
rheumatic heart disease, 832
spectrum, 841
symposium on, 828
treatment of, 828, 836, 841
anticoagulants, 843, 854, 857
arrhythmias, 842, 857
bed rest for, 852
congestive heart failure, 842, 857
digitalization, 842, 857
diuretics, 854
potassium, 854
sodium restriction and diuretics, 842
steroids, 843, 854, 858
x-rays of heart, 840

Pronethalol
and oxygen consumption of new-born rabbits, *321*
for treating tachycardia, 778

Propranolol
double-blind trial of, in angina of effort, *155*
effect in angina pectoris, *154*
in treatment of hypertension, *320*

Protein-losing enteropathy
secondary to constrictive pericarditis, *318*

Prostheses
mitral valve
red blood cell survival, 570
University of Cape Town prothesis, 721
Starr-Edwards ball valve
red cell survival, 570
results of, *494*

Puerperium
idiopathic myocardiopathy of, 19

Pulmonary artery
atresia
coronary artery-right ventricular fistula, 582
banding, 172
bifidity
Ehlers-Danlos syndrome, 602
embolism. *See* Embolism, pulmonary
hypertension
pulmonary artery banding, 172
thrombosis, 377
mitral insufficiency due to anomalous origin of left coronary artery from, *150*
pressure
role of hydrogen ion concentration, 788
stenosis. *See* Stenosis, pulmonic
thrombosis, 377
See also Cor pulmonale

Pulmonary disease
idiopathic unilateral increased pulmonary luminosity with hypovascularization, *492*
"primary" pulmonary hypertension and Raynaud's phenomenon, *491*

Pulmonary regurgitation
immediate diastolic murmur, 797

Pulmonary valve
insufficiency
phonocardiographic differentiation of aortic and, 352

Pulmonary veins
anomalous pulmonary venous return, 406
total anomalous pulmonary venous connection, electro-vectorcardiographic, hemodynamic, and anatomic correlations, *150*

Pulses
pedal, *662*
subclavian steal syndrome, 346
work speed as measure of exercise stress in subjects of different weights, 940

Q

QRS complexes
factor analysis of electrocardiograms, 274

QRS loop
total anomalous pulmonary venous connection, *150*

Quinidine
digitalis intoxication following conversion to sinus rhythm, 58
effects on auricular fibrillation in asymptomatic young man, *657*

Quinine poisoning
electrocardiograms, *321*

R

Radiocardiography
isotope technics, 309
supine exercise, 361

Radioelectrocardiograms
fetal heart sounds, *317*

Radiographs
hyperbaric chamber, *663*

Radioisotopes
cardiac output by external radioisotope counting in atrial fibrillation, *659*
determination of coronary flow with a positron emitter (rubidium-84), 636
renogram
used in detection of disparate kidney function in hypertensive patients, 5

Raynaud's disease
"primary" pulmonary hypertension and, *491*

Rebound phenomenon
after discontinuation of anticoagulation therapy after myocardial infarction, 878

Recording techniques
heart sounds, *156*
precordial movements over right ventricle
in children with pulmonary stenosis, 241
in normal children, 232

Recosen
effects on myocardial explants, *320*

Red blood cells
induction of arterial lipogenesis by, *660*
survival following aortic valvular disease, 570

Renal artery
assessment of curable renovascular hypertension by radiographic technics, *318*
stenosis. *See* Stenosis, renal artery

Renal baroreceptor
control of acute renin release in normotensive, nephrogenic and neurogenic hypertensive dogs, *1052*

Renal complications
after cardiac surgery, 614

Renal disease
unilateral
hypertension and, 682
use of I^{131}-Hippuran renogram in the detection of disparate kidney function in hypertensive patients, 5

Renal function
in patients undergoing replacement of aortic valve, 394

Renal ischemia
renovascular hypertension due to, 1

Renin
assay of, in single glomeruli in normal rabbit, *1051*
measurement of, 513
renal baroreceptor control of acute renin release in normotensive, nephrogenic and neurogenic hypertensive dogs, *1052*

Renograms, radioisotope
used in detection of disparate kidney function in hypertensive patients, 5

Reserpine
value of chlorthalidone plus, in moderately severe and severe hypertension, 13

Respiration
and circulatory studies in myocardial infarction and cardiogenic shock, *154*

Rest
effect on heart rate, 549

Return to work
after cardiac infarction, *155*
with myocardial infarction, *152*

Rheumatic fever
carditis
diagnostic test for, 925
diagnosis
Jones criteria (revised) for, 664
method for culturing beta hemolytic streptococci from the throat, *1054*
recurrences in patients not receiving continuous prophylaxis, *493*
U. S. and U. K. joint report on, 457
use of ACTH, cortisone and aspirin, 457

Rheumatic heart disease
coarse atrial fibrillation, 290
U. S. and U. K. joint report on, 457
use of ACTH, cortisone and aspirin, 457

Rhythm
atrial reciprocal, 687
paired electrical stimulation, 677
sinus. *See* Sinus rhythm

Roentgenology
cardiopulmonary response to the injection of angiographic contrast medium, *494*
coronary arteriography, *493*
ST segment of ventricular complex in extremity leads, *316*
stroke, 559
Vascular Roentgenology (Schobinger and Ruzicka, ed.), 1041

Roster
Subspecialty Board of Cardiovascular Disease of the American Board of Internal Medicine, 499

Rubidium-84
determination of coronary flow with a positron emitter, 636

S

Salt loading
hypertension due to renal artery stenosis, 888

Sclerosis, coronary
heart muscle clearance in, *1046*

Scotland
coronary heart disease in elderly men, 153

Septal defects
abnormal arteriovenous communications, 1001
atrial
atrioventricularis communis, clinical aspects and surgical treatment, *151*
electrocardiogram and frontal vectorcardiogram in ostium secundum defect and endocardial cushion defect, *149*
immediate diastolic murmurs, 797
Lutembacher syndrome, 589
persistent common atrioventricular canal, anatomy and function, 120
total anomalous pulmonary venous connection, *150*
interventricular
persistent common atrioventricular canal, anatomy and function in relation to surgical repair, 120
ventricular
atrioventricularis communis, clinical aspects and surgical treatment, *151*
and cardiac failure in infants, *150*
due to penetrating wound of heart, 995
infants, *152*, *861*
multiple muscular, 35
postinfarction, 76
pulmonary artery banding, 172
surgical treatment of, associated with pulmonary hypertension, *495*

Septum
intact ventricular
coronary artery-right ventricular fistula, 582
interventricular
rupture of, 76
ventricular
multiple muscular defects, 35
myocardial biopsy utilizing, *663*
postinfarction ventricular septal defect, 76
severe pulmonic stenosis with intact, and right aortic arch, 114

Serum
enzymes
in clinical diagnosis, 1010
myocardial infarction, *1046*
lactic dehydrogenase level
diagnostic test for carditis in rheumatic fever, 925
lipids
effects of exercise on, *859*
essential fatty acids in, of young male rural Guatemalans and urban North Americans, 106

Shock
bacteremic
hypothermia in, *322*
circulatory and respiratory studies in myocardial infarction and cardiogenic, *154*
hemorrhagic necrosis, 332

Shunts
hemodynamic basis for clinical manifestations of patent ductus arteriosus, *151*
left-to-right
krypton-85 in detecting intracardiac, 134
pulmonary artery banding, 172
spread to appearance time ratio in the estimation of, *490*
use of indicator-dilution technics, 772

Siblings
with cardiac glycogenosis, *318*

Sinus
effect of halothane on carotid sinus baroreceptor activity, *322*

Sinus rhythm
acute effects of countershock conversion of atrial fibrillation upon right and left heart hemodynamics, 214
cardiac output by external radioisotope counting in patients reverted from atrial fibrillation, *659*
digitalis intoxication following conversion to, 58

Smoking
relationship to heart disease, *1045*
stroke volume and cardiac output after, *491*

Sodium
body water and electrolyte composition in cardiac failure, 169
exchangeable body potassium, body water in previously edematous patients, 185
method for detention and quantification of impaired excretion, 223
oral tolerance test, 223
role of bradycardia in retention of, *862*

Sodium citrate salts
potassium citrate salts and, for digitalis toxicity, *320*

Sodium diphenylhydantoin
in treatment of arrhythmias, *656*, *657*

Sounds, heart
effect of stethoscope-applied pressure in auscultation, 430
new portable recording system, *156*
use of frequency multiplication for fetal, *316*
tape recorded
detection of heart disease
Chicago area high school study, 966
Michigan City study, 956

South African Bantu
annular subvalvular left ventricular aneurysms, 43

Spectrophotometer
fibre optics, for in vivo oximetry, *1048*

Splanchnic circulation
effect of digoxin in, 524

ST segment
electrocardiograms, *316*

Standards
for cardiac diagnostic and surgical centers, 497

Starling curve
descending limb of, and failing heart 871

Stenosis
aortic
blood flow, 251
calcification in vascular grafts, *494*
congenital, *661*
surgical management of, *496*
effect of nitroglycerin on left ventricular wall tension in fixed orifice, 204
results of surgical treatment for diffuse subvalvular, 52
subvalvular, technique for correcting, 52, *496*
supravalvular, *149*
surgery, 732
surgical one-stage correction of supravalvular, and coarctation of aorta, *495*
use of amyl nitrite in assessment of, *661*
Aortic Stenosis (Cullhed), *1034*
congenital valvular
long-term postoperative follow-up, 732
hypertrophic subaortic
pressure gradients without obstruction, 881
mitral
behavior of left atrial pressure and simultaneously measured left ventricular diastolic pressure, *491*
coarse atrial fibrillation, 290
Lutembacher syndrome, 589
patients with systemic emboli and, *661*
pulmonic and aortic insufficiency, 352
replacement of "parachute deformity," in children, 130
serious, with slight symptoms, *660*
muscular subaortic
due to ventricular septal hypertrophy, *156*
poststenotic dilation of the aorta, *662*
use of amyl nitrite in assessment of, *661*
pulmonary
coronary artery-right ventricular fistula, 582
infundibular, *150*
late response to correction of, 258
precordial movements over right ventricle in children with, 241
severe, with intact ventricular septum and right aortic arch, 114
renal artery, 682
hypertension due to salt loading in, 888
tricuspid
fibroma of right ventricle producing, 451

Steroids
Steroid Analysis by Gas Liquid Chromatographs (Patti and Stein), *1040*
treatment of primary myocardial disease, 843, 854, 858

Stethoscopes
effect of applied pressure in auscultation, 430

Stokes-Adams disease
concealed AV conduction, 386
congenital familial cardiac conduction defects, 32

Streptococcal infections
diagnosis of rheumatic fever, 664
method for culturing beta hemolytic streptococci from the throat, *1054*

Stress, cardiac
free nucleotides in myocardium of rats undergoing, *492*
use of heart rate during exercise, 622

Stroke
medical and surgical care, 559

Stroke volume
and cardiac output after smoking, *491*

Subaorta
hypertrophic
pressure gradients without obstruction, 881
muscular stenosis, *662*
due to ventricular septal hypertrophy, *156*
poststenotic dilation of the aorta, *662*
use of amyl nitrite in assessment of, *661*

Subclavian artery
hemodynamics of the upper extremities
subclavian steal syndrome, 346
syndrome, 346

Subcutaneous nodules
diagnosis of rheumatic fever, 664

Subvalvular aortic stenosis
results of surgical treatment, 52

Supravalvular aortic stenosis, *149*

Supraventricular arrhythmias
use of diphenylhydantoin sodium, *657*

Surgery
advanced ischemia, *662*
aortic stenosis, 732
arterial reconstruction, 515, 517
atrioventricularis communis, *151*
bonding agents, *496*
calcification in vascular grafts in operated aortic isthmic stenosis, *494*
circulatory and acid-base changes during operations for abdominal aortic aneurysm, *494*
congenital aortic stenosis, *496*
congenital aortic valvular stenosis, 732
congential heart lesions in adults, *495*
cor triatriatum, *152*
coronary artery disease, *152*
dacron vascular grafts, *495*
diffuse subvalvular aortic stenosis, 52
effects of, under general anesthesia on electrocardiograms in ischaemic heart disease and hypertension, *153*
Fallot's tetralogy, *495*
total correction, relationship between polycythemia and surgical mortality, 65
fibroma of right ventricle, 451
hemorrhagic necrosis of the gastrointestinal tract, 329, 332
for hypertension
adrenalectomy and sympathectomy, *320*
left ventricular function after resection of papillary muscles in mitral valve replacement, *494*
mastectomy
electrocardiogram after, 746
medical complications after, 608
arrhythmias, 608
congestive heart failure, 612
electrolyte disturbances, 613
gastrointestinal bleeding, 617
hemolysis, 617
hemorrhagic diathesis, 617
hypertension, 618
infections, 616
involving central nervous system, 614
low cardiac output syndrome, 612
postperfusion syndrome, 617
postpericardiotomy syndrome, 617
pulmonary complications, 616
renal complications, 614
mitral valve replacement, *494*
"parachute deformity" in children, 130
University of Cape Town prosthesis, 721
multiple muscular ventricular septal defects, 35
one-stage correction of supravalvular aortic stenosis and coarctation of aorta, *495*
open heart
aortic valve replacement, 394
effects of myocardial hypothermia or coronary perfusion, 372
late response to correction of pulmonary stenosis, 258
penetrating wound of heart, 995
pericardiectomy for constrictive pericarditis, 415
persistent common atrioventricular canal, anatomy and function in relation to repair, 120
popliteal aneurysms, 517
postinfarction ventricular septal defect, 76
pulmonary artery banding, 172
reconstruction of two-coronary system with dacron graft, 293
removal of foreign bodies, 782
right ventricle, total obstruction, *151*
rupture of interventricular septum, 76
severe pulmonic stenosis with intact ventricular septum and right aortic arch, 114
single left coronary artery with fistula to right ventricle, 293
standards for cardiac diagnostic and surgical centers, 497
stroke, 559
subvalvular aortic stenosis, *496*
thromboendarterectomy, 377
thrombosis of pulmonary arteries, 377
tricuspid atresia, 977
valvuloplasty
late response to correction of pulmonary stenosis, 258
vascular anastomosis–sutures, staples, or glue, *496*
ventricular septal defect associated with pulmonary hypertension, 495

Sutures, *496*

Sympathectomy, 517
for hypertension, *320*

Syndromes
bacteremic shock, *322*
Ehlers-Danlos, 602
floppy valve, 897
low cardiac output, 612
Lutembacher, 589
Marfan syndrome, 896
postperfusion, 617
postpericardiotomy, 617
straight back, 193
stroke, 559
subclavian steal, 346
trisomy-18, 802

Systole
abnormal precordial pulsation in patients with myocardial infarction, 650
atrial
influence of digitalization on contribution of, to cardiac dynamics at fixed ventricular rate, 84

T

Tachycardia
beta-adrenergic blockade, 778
disturbances or rate, rhythm and conduction in acute myocardial infarction, *657*
paroxysmal
reciprocal rhythm and, 702
prolonged ventricular, treated by external countershock, *658*
treatment by external electric shocks, *658*

Tamponade, cardiac
cardiac perforation following left ventricular cineangiocardiography, 593

Techniques
kinetocardiographic changes in ischemic heart disease, 650
myocardial biopsy, utilizing ventricular septum, *663*
oral sodium tolerance tests, 223

Tetralogy of Fallot. *See* Fallot's tetralogy

Thoracic deformities
straight back syndrome, clinical cardiovascular manifestations, 193

Thromboembolism
after cessation of long-term anticoagulants, 878
linolenic acid for prevention of, *861*
pulmonary arteries, 377

Thromboendarterectomy, 377
advanced ischemia, *662*

Thrombosis
calcification of carotid siphon, 538
focal cerebral ischemia, 438
Hemorrhage and Thrombosis. A Practical Clinical Guide (Salzman and Britten, ed.), *1039*
hemorrhagic necrosis of the gastrointestinal tract, 329
incidence in myocardial infarction, *153*
linolenic acid for prevention of, *861*
pulmonary arteries, 377

Thyroid, The (Hazard and Smith, ed.), *1041*

Transposition of great vessels
diagnosis, *862*
inverted malformations in corrected, 298

Triamterene
congestive heart failure treated with, *863*
metabolic studies, in patients with cirrhosis and ascites, *862*

Tricuspid valve
atresia
palliative surgery for, 977

Trisomy-18 syndrome
origin of both great vessels from right ventricle, 802

Tumors
diagnosis of pheochromocytoma and neuroblastoma, *492*
fibroma of right ventricle producing severe tricuspid stenosis, 451
strokes and, 559

U

University of Cape Town prothesis, 721
hemodynamic findings following, 721

Urine
osmolality
aortic valve replacement, 394

V

Vagovagal syncope
associated with diffuse esophageal spasm, *658*

Valves, cardiac
floppy valve syndrome, 897
insufficiency,
during catheterization, *491*
myxomatous transformation, 897
nomogram for estimation of, 425

Valvotomy and valvuloplasty. *See* Surgery, cardiac

Vanilmandelic acid
diagnosis of pheochromocytoma and neuroblastoma, *492*

Vascular disease
abdominal aortic aneurysm with vena caval fistula, *663*
advanced ischemia, *662*
arteriovenous fistula of internal iliac artery and vein, related to trauma at childbirth, *662*
cerebral ischemia, *662*
mesenteric arterial insufficiency and abdominal angina, *663*
stenoses of arteries of the lower extremity, *662*

Vascular system
Vascular Roentgenology (Schobinger and Ruzicka, ed.), *1041*

Vectorcardiograms
changes produced by electrical stimulation of cardiac nerves, *492*
combined ventricular hypertrophy, 265
factor analysis, 274
frontal
ostium secundum defect and endocardial cushion defect, *149*
horizontal plane electrocardiographic vectors, study in conjunction with frontal projections, *1050*
pseudo P pulmonale, 96
right bundle branch block, *317*
total anomalous pulmonary venous connection, *150*
U vector loop, right ventricular hypertrophy, right bundle branch block and myocardial infarction, *317*
ventricular gradient determined with Frank's lead system and relation to heart rate change, *317*

Veins
anomalous pulmonary venous return, 406
autogenous
grafts, 515, 517
forearm
effect of nitroglycerin and amyl nitrite on, 755
origin of blood withdrawn from forearm, during rhythmic exercise, 489
pulmonary. *See* Pulmonary veins
saphenous vein bypass, *662*
total anomalous pulmonary venous connection, *150*

Vena cava
fistula
abdominal aortic aneurysm with, *663*

Ventricles
arrhythmias
diphenylhydantoin sodium, *657*
fibrillation
reduction by hyperbaric oxygenation of the mortality from, following coronary artery ligation, *656*
hypertrophy
combined, 265
left
annular subvalvular aneurysms, 43
cardiac perforation following cineangiocardiography, 593
effect of supine exercise on volume, and oxygen consumption, 361
function after resection of papillary muscles in total mitral valve replacement, *494*
muscular architecture, 301
septal hypertrophy, electrocardiogram in muscular subaortic stenosis due to, *156*

wall tension, effect of nitroglycerin on, in fixed orifice aortic stenosis, 204
premature beats
diagnosis of septal infarction, *1048*
response in atrial fibrillation, 69
right
coronary artery-right ventricular fistula, 582
diagnosis and surgical correction of total obstruction, *151*
fibroma producing severe tricuspid stenosis, 451
hypertrophy
in people born and living at high altitudes, *1053*
origin of both great vessels from, with the trisomy-18 syndrome, 802
precordial motion over, in children with pulmonary stenosis, 241
precordial movements over, in normal children, 232
single left coronary artery with fistula to, 293
septal defects. *See* Septal defects, ventricular
septum
aneurysms, 981
intact, severe pulmonic stenosis with, and right aortic arch, 114
volume
indicator dilution studies, *316*

Vertebral artery
subclavian steal syndrome, 346

W

Warfarin
compared with bishydroxycoumarin, *860*

Water, body
electrolyte composition in cardiac failure, 169
exchangeable sodium, body potassium and, in previously edematous patients, 185
retention of
role of bradycardia, *862*

Weight
work speed as measure of exercise stress in subjects of different, 940

Work speed
as measure of exercise stress in subjects of different weights, 940

X

X-rays
calcification of carotid siphon, 538

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to

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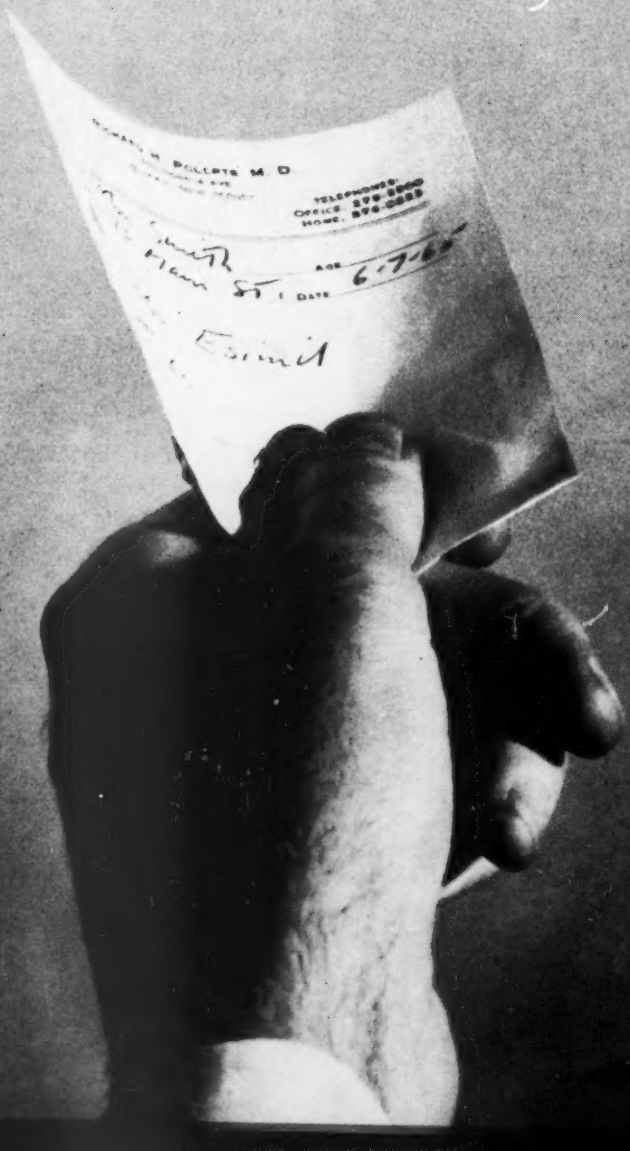

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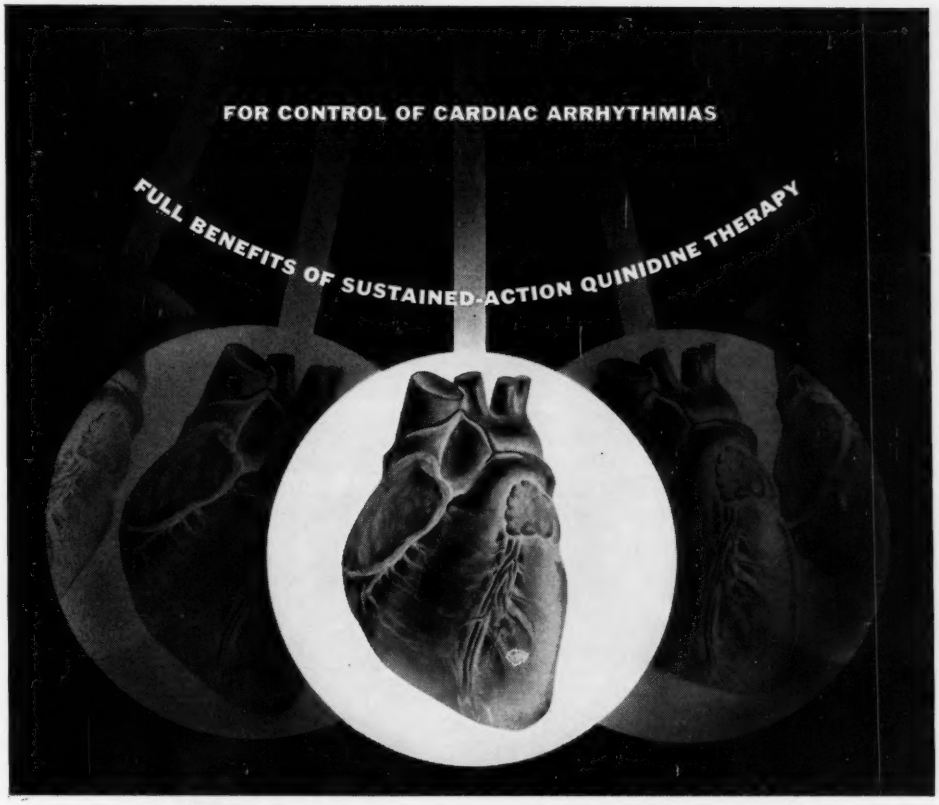

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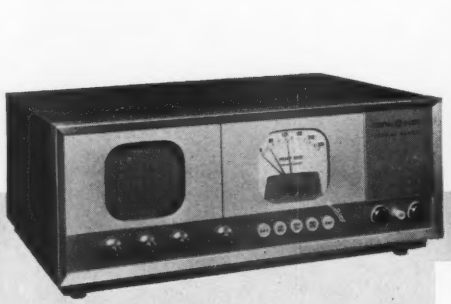

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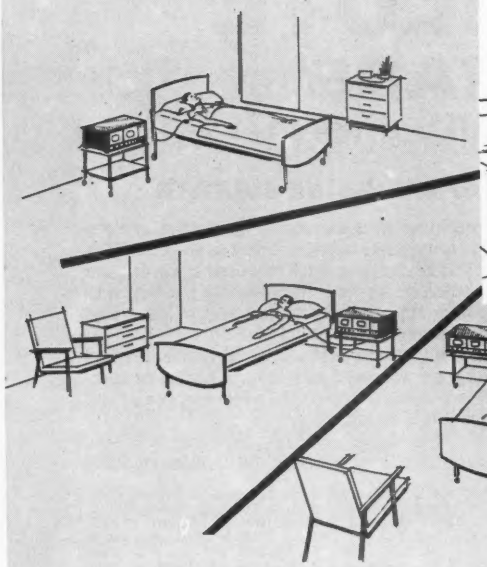

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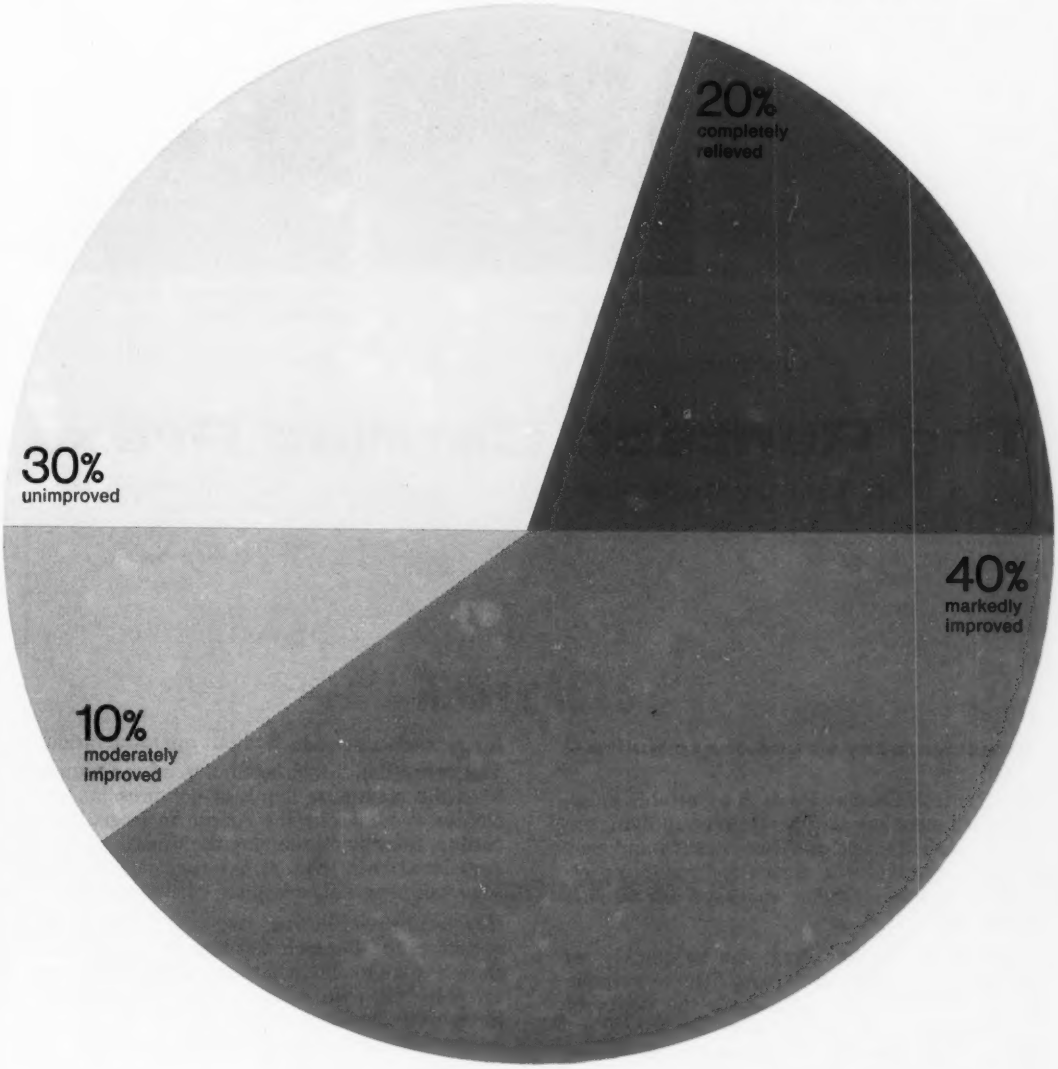

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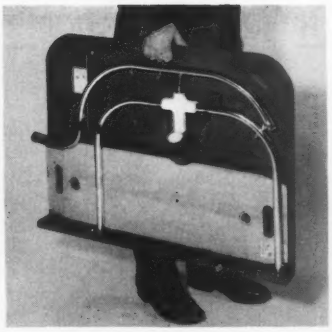

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38th Scientific Sessions

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19th Annual Meeting, Council on Arteriosclerosis—

American Society for the Study of Arteriosclerosis

Bal Harbour, Miami Beach, Florida

October, 1965

ABSTRACTS

CONTENTS

Council on Arteriosclerosis—American Society for the Study of Arteriosclerosis II-1

Scientific Sessions of the American Heart Association II-39

Author Index II-225

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BAL HARBOUR, MIAMI BEACH, FLORIDA

OCTOBER 13-14, 1965

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19th Annual Meeting

ABSTRACTS

Depletion and Repletion of Heparin-released Lipase in Normal and Diabetic Rats

Edip Aktin and H. C. Meng, Nashville, Tennessee

Depletion and repletion of the heparin-released lipase in normal and alloxan-diabetic rats were studied using isolated perfused hearts, heart slices and homogenates, and plasma of whole animals. Lipase activity was expressed as μmole free fatty acid (FFA) release/g tissue/hr, using a triglyceride emulsion as a substrate. Normal and diabetic rat hearts perfused with heparin (10 μg/ml) showed no significant difference in perfusate lipolytic activity. However, when normal rats were given heparin (1 mg/kg, iv) ten minutes before hearts were perfused with heparin, the lipase activity was reduced to 19.4 μmoles FFA as compared with 43.5 obtained in rats given no heparin. Under the same experimental conditions, the lipase activities from hearts of diabetic rats with and without heparin pretreatment were 5.6 and 42.1 μmoles respectively. The lipase activity from perfused hearts of normal rats taken two hours after heparin was 31.4 μmoles FFA (72% of 43.5) and reached the maximum of 60.0 (137% of 43.5) after four hours. In diabetic rats the perfusate lipase activity was only 9.3 μmoles FFA two hours after heparin and it was not greater than 29.3 even eight hours after heparin. Similar results were observed in heart slices and homogenates and whole animals. It is concluded that heparin injection caused more marked depletion of the heparin-released lipase, and the rate of repletion was slower in diabetic than in normal rats.

Comparison of Plasma Lipids of Normal Young and Middle-aged Males

Roslyn B. Alfin-Slater, Lillie M. Grossman, Hiroyasu Fukuba, and H. Joseph Hernandez, Los Angeles, California

To investigate possible changes in plasma lipids which may occur with age, blood plasmas from two groups of men, group I consisting of nine college students (ages 19 to 22), and group II consisting of nine college professors (ages 42 to 55), subsisting on self-selected diets, were analyzed for total lipids, cholesterol, lipid distribution, and fatty acid composition of three isolated lipid fractions. There was a statistical difference in total lipid content between the two groups: values in the younger group were 478 ± 140 mg%; in the older group, 898 ± 131 mg%. Similar differences were observed in total cholesterol values, which averaged 151 ± 46 mg% for the younger group, and 226 ± 26 mg% for the older group. In spite of these changes, no significant differences were observed in lipid distribution; the percentages of cholesterol esters, triglycerides, and phospholipids were 32.4 ± 1.6, 27.9 ± 3.8, and 25.9 ± 4.8 for the younger population, and 31.6 ± 3.5, 26.3 ± 4.5, and 28.4 ± 2.9 for the older men. Determinations of the fatty acid composition of each fraction revealed significant differences in oleic and arachidonic acids in the triglyceride fraction of the younger group as compared with the older group, but no differences in fatty acid composition of sterol esters and phospholipids. Whether the higher total cholesterol and lipid values seen in the older group result from simple aging, or whether other variables, e.g., differences in dietary preferences, physical activity, accumulated physical and physiological stresses etc., are primarily involved, needs further study.

Is Digitalis Necessary in the Geriatric Cardiac Patient?

Saul P. Baker, Cleveland, Ohio

For almost 200 years, digitalis and its derivatives have been used empirically in the therapy of congestive heart failure in man. Similarly, toxic effects of digitalis, both on the myocardium and extracardiac, have also been extensively observed and reported. However, the dogma of prophylactic and/or maintenance digitalis therapy in patients who have suffered episodes of congestive heart failure has become so firmly inbedded in the therapeutic armamentarium of the phy-

sician, that cardiologists still prescribe cardiac glycosides for prophylactic and/or maintenance therapy in congestive heart failure.

In geriatric patients, toxic manifestations of excess digitalis effect may be insidious and bizarre, and may be completely overlooked unless specifically sought for. Furthermore, the universal need for prophylactic and/or maintenance digitalis therapy in geriatrics is questioned (1) in view of its toxic effects, and (2) the fact that geriatric patients may be maintained ambulatory and at usual activity without the use of cardiac glycosides for long periods of time after suffering one or more acute episodes of congestive heart failure.

By correcting the basic pathophysiological mechanisms of congestive heart failure, namely, the increase in sodium ion concentration, increase in extracellular fluid compartment, and increase in circulating blood volume, as well as frequently concomitant hypokalemia, it has been possible to maintain geriatric patients ambulatory and at normal activity in the community without the use of digitalis for periods now ranging up to more than one year. All of these geriatric patients had manifested toxic symptoms of excess digitalis effect; all had experienced one or more episodes of acute congestive heart failure; and all suffered from chronic congestive heart failure.

Mechanism of Hyperglyceridemia in Hawaiian and Japanese Males

David R. Bassett and Robert C. Moellering, Jr., Honolulu, Hawaii

To evaluate the relationship of possible active endogenous lipogenesis to hyperglyceridemia as seen in Japanese and Hawaiian males with and without ECG-proven myocardial infarction, plasma was ultracentrifuged at 4 C for 0.4×10^6 G-minutes, and "primary" particles removed; then at 3×10^6 G-minutes, and "secondary" particles removed (terminology implies that method may give incomplete separation of classes). The triglyceride (TG) and cholesterol ester (ChE) fractions of both particle classes were separated by thin-layer chromatography, and their respective fatty acid patterns analyzed.

Evidence for active endogenous lipogenesis (increasing percentage of 16:0, 16:1, and 18:1, and decreasing 18:2 and 20:4 fatty acids) is noted in the ChE fraction of "secondary" particles, when related to increasing fasting serum triglyceride concentration (up to 149 mg%, 150 to 199, 200 to 399, and above 400 mg%; $n = 14$, 6, 20, and 10 specimens respectively). (Evidence for differing identity of "primary" and "secondary" classes was found, namely, increased percentage of 16:0, and decreased 18:2 and 20:4 in "primary" ChE particles, these therefore being intermediate between the typically described pattern for TG and ChE.)

No relationship of TG and ChE fatty acid pattern was noted to total serum cholesterol concentration or age. Neither were consistent differences seen in comparing Japanese with Hawaiian subjects, or cases with controls, suggesting that hyperglyceridemia, when it exists in either racial group, may have a similar pathogenesis, and that the underlying mechanism is often overactive endogenous lipogenesis. Evidence also exists that dietary fat is retained as a secondary phenomenon.

Effects of Hypertriglyceridemia on Urinary Uric Acid Outputs

Donald Berkowitz and Sol Glassman, Philadelphia, Pennsylvania

We have previously demonstrated a positive correlation between the blood uric acid and triglyceride levels rather than with the cholesterol. Although the exact mechanisms involved in this relationship are not known, a renal factor has been suggested. The purpose of this study was to determine the effects of fat-induced hypertriglyceridemia on the urinary excretion of uric acid.

Twenty hospitalized patients were observed during three dietary periods. The first consisted of three to five days of a normal diet, during which the daily fat intake was 75 g. Following this, they were maintained for five days on a frequent milk-cream feeding regimen, during which the daily fat intake approximated 200 g. Thereafter a normal diet was again administered for three to five days. Fasting blood samples were taken at one- to two-day intervals for the determination of triglycerides and uric acid. Daily 24-hour urine collections were analyzed for uric acid.

During the period of high-fat feedings, there was a prompt and progressive increase in the triglyceridemia reaching grossly lipemic levels in many patients. The blood uric acid levels showed a parallel increase, with hyperuricemia resulting in over half of those with normal values initially. Urinary uric acid excretion decreased significantly during this interval. The hematocrit, blood glucose, and endogenous creatinine clearance remained unchanged, and the ratio of uric acid clearance to creatinine clearance paralleled urinary uric acid output. When normal feedings were resumed, the blood uric acid and triglycerides and urinary uric acid outputs returned to control values.

The data thus give positive evidence for a renal factor directly dependent on the degree of

triglyceridemia as a mechanism in the hyperuricemia associated with hypertriglyceridemia.

Studies on the Mechanism of the Hypolipemic Action of Dietary Calcium in Man

Marvin L. Bierenbaum, Harold Yacowitz, and Alan I. Fleischman, Montclair, New Jersey

A previous report indicated that ingestion of 0.9 g calcium in addition to normal dietary calcium exerted both a hypocholesterolemic and hypotriglyceridemic effect on free-living humans. Similar results were noted in several species of animals. Preliminary studies showed that the hypocholesterolemic effect could occur within four days. It had been presumed that these changes were due to the steatorrhea resulting from the ingestion of high levels of dietary calcium and that the hypolipemic effect was the result of the preferential fecal excretion of saturated fatty acids, while permitting more unsaturated fatty acids to be absorbed.

Eight adults on an *ad libidum* diet, between the ages of 20 and 50 years, five males and three females, ingested 0.9 g excess calcium either as the carbonate or the gluconate for 21 days. A 14-day benchmark period preceded the experimental period. Serum free fatty acids (FFA) were determined by vapor phase chromatography at seven-day intervals during both the benchmark and experimental periods. The serum FFA P/S ratio had previously been shown to change with diet within 72 hours. Results indicated a completely random distribution of FFA P/S ratios. In some cases, the P/S ratio showed a higher degree of saturation during the experimental period than during the benchmark period. This occurred despite the fact that the group serum cholesterol and triglyceride levels were lowered by a mean of 13.5 mg%, SD = 5.1, and 24.8 mg%, SD = 14.4, respectively. Thus, the hypolipemic action of dietary calcium appears not to be due primarily to the preferential fecal excretion of saturated fatty acids.

Modified Fat Dietary Management of the Young Coronary Male: A Five-Year Controlled Study (P)

Marvin L. Bierenbaum, Donald P. Green, Alvin Florin, Alan I. Fleischman, and Anne B. Caldwell, Montclair, New Jersey

One hundred male patients between the ages of 20 and 50 years with documented myocardial infarctions and under dietary management with a 30% fat diet (relatively high in polyunsaturated fatty acids) were matched to an identical nondietary-treated coronary group, and followed for five years to assess morbidity and mortality rates. The comparability of these two groups was defined with regard to age, age at time of infarction, number of infarctions, prevalence of hypertension, degree of angina, height and weight, and serum cholesterol level. The study group showed an incidence rate per 100,000 of 4,450 for new infarctions and 2,108 for deaths from infarction. The control group showed an incidence rate per 100,000 of 7,143 for new infarctions and 4,911 for deaths from infarction. The nondietary-managed group had a 160% higher infarction rate and a 233% higher mortality rate than the study group. Both figures were highly significant at the 1% level. The mean serum cholesterol in the group on the 30% fat diet changed from 259 mg% on admission to 235 mg% at the time of evaluation. It is concluded that controlled fat dietary management is a significant factor in lowering, first, serum cholesterol and, second, the morbidity and mortality from coronary heart disease.

Exertion and Acute Coronary Artery Injury

Asher Black, Martin M. Black, Goffredo, G. Gensini, and Salvatore Di Giorgi, Syracuse, New York

The relationship between exertion and acute coronary injury is investigated as to the pathophysiological sequence of events. Five cases of acute myocardial infarction following very strenuous exertion are presented. Two patients came to postmortem examination, and the pathology of the coronary artery lesions is reviewed. The nature, evolution, and location of coronary artery plaques and their relationship to the hemodynamics and motion of coronary arteries was investigated. Within the life cycle of coronary artery plaques, changes can take place during which they may be more susceptible to internal hemorrhage and fracture. The relationship of acute coronary artery injury by internal hemorrhage into the plaque or fracture is correlated with coronary artery motion as seen on coronary cinearteriography during the resting state and following the administration of isoproterenol. Coronary artery motion consisting of pulsations, stretching along the long axis (accordion action), and spiral twisting is seen. There is also a whip-like action of the coronary arteries with the fulcrum of the whip being localized in the area where the usual occluding coronary plaques appear. The concept that this unique motion of coronary arteries in the patient with vulnerable plaques under the influence of strenuous exertion may result in acute coronary artery injury and coronary artery spasm or occlusion is developed.

A short run of coronary cinearteriography demonstrating various motions of coronary arteries will be presented.

Estimation of Human Hypercoagulability by a Method of Measuring Blood Flow (P)

Edwin Boyle, Jr., Clifford R. Talbert, Jr., Lola F. Engler, and Ismael B. Morales, Charleston, South Carolina

The thrombotic tendency in humans has been investigated. Following stylused needle venipuncture, blood passively flows through a .031 inch I.D. polyethylene tubing into a measuring tube. Coagulability was analyzed according to three criteria: (a) blood flow deceleration (break time); (b) time when blood flow ceases (thrombus time); (c) total blood collected (volume). Histological examination of specimens demonstrated classical thrombus accumulation of interlacing fibrin in the tubing.

Analysis of 316 observations in 96 diseased and 63 observations in 31 normals revealed the following differences: Among 15 *diabetics,* 43 observations yielded a thrombus time 15% shorter than normals (18.4/21.5 min, $P = < .01$); break time 18% shorter (13.1/16.0 min, $P = < .01$); volume, 6.9/7.0 ml, not significant. Among 25 subjects with *arteriosclerosis obliterans,* 81 observations revealed thrombus time 16% shorter than normals (18.0/21.5 min, $P = < .02$); break time 17% shorter (13.3/16.0 min, $P = < .01$); volume 28% less (5.0/7.0 ml, $P = < .01$). Among four subjects with *clinical thrombosis of less than six weeks' duration* who were not on warfarin anticoagulants, 11 observations yielded thrombus time 44% shorter than normals (12.0/21.5 min, $P = < .01$); break time 52% shorter (7.6/16.0 min, $P = < .01$); volume 43% less (4.0/7.0 min, $P = < .01$). Adequate warfarin anticoagulants prolonged thrombus time, except in two hyperlipemics with acute thrombosis and marked shortening of all measurements. Lee-White times and hematocrits in diseased subjects were not significantly different from normals.

These data suggest that a measured blood flow method may be useful in detection of clinical hypercoagulability.

Blood Coagulation, Fibrinolysis, and Hyperlipemia

Paul W. Boyles, Berwyn, Pennsylvania

There are conflicting data reported as to the effects of blood lipids upon coagulation and fibrinolysis. The measurements of these two physiological functions in four patients with extreme elevation of total cholesterol and beta-lipoprotein form the basis of this report.

The following methods were used: clotting tendency by the thromboplastin generation accelerator test of Spittel, et al., fibrinolysis by the streptokinase heated fibrin plate assay, cholesterol by the method of Ferro and Ham, and beta-lipoprotein by the immocrit technique of Heiskell, et al. The normal variations of these tests with age and sex were determined in 194 healthy blood donors.

The sera from four patients with cholesterol values between 428 and 1,408 mg % demonstrate marked inhibitory effects upon thromboplastin generation without significant alterations in fibrinolysis.

These data suggest that extreme hypercholesteremia induces hypocoagulability rather than hypercoagulability and reduced fibrinolysis previously reported to be a factor in the development of atherosclerosis.

Interaction of Dietary Cholesterol and Polyunsaturates in Practical Diets for Serum Cholesterol Reduction (P)

Helen B. Brown, Marilyn E. Farrand, and Irvine H. Page, Cleveland, Ohio

The role of cholesterol in fat-controlled diets is more important than generally recognized. The amount permissible in practical diets is of concern because inclusion of two egg yolks a day in an otherwise adequate diet nullifies its hypocholesteremic effect. In a series of quantitative, 18-day tests, 50 free-living, normo-cholesteremic persons were fed a standard diet and one or more variants. The standard diet contained 200 mg cholesterol, 2,700 calories, with 38% of calories as fat, low in saturates (11%) and high in polyunsaturates (17%). The average serum cholesterol reduction with the standard diet was 40 mg/100 ml. Variant diets were also low in saturates and contained either 200 mg or 550 mg at four levels of polyunsaturates, 14%, 15%, 17% or 23%, and 450 mg cholesterol with 15% polyunsaturates. Serum cholesterol reduction with variant and standard diets was compared in the same subject.

With 200 mg cholesterol, 15% or more polyunsaturates were required for serum cholesterol reduction similar to that with the standard diet; 450 mg cholesterol just exceeded the critical limit in a diet with 15% polyunsaturates. Eleven of 23 subjects had a reduction in serum cholesterol similar to that with the standard; 12 had much less. With 550 mg cholesterol, only 23% polyunsaturates supported reduction similar to the standard; 14% to 17% did not. Thus, diets containing 15% polyunsaturates reduce serum cholesterol levels adequately with 200 mg cholesterol, may or may not be effective with 450 mg, and are ineffective with 550 mg. The higher the dietary cholesterol, the more polyunsaturates are required. The fat composition of these diets was attained with available foods. Practical hypocholesteremic diets may contain

300 to 350 mg cholesterol from meat, fish, and eggs, and should also have at least 15% polyunsaturates, preferably more.

Osseous Xanthomatosis with Pathological Fractures in Carbohydrate-accentuated Hyperglyceridemia

Osvaldo J. Brusco, R. Palmer Howard, Joe B. Jarman, and Robert H. Furman, Oklahoma City, Oklahoma

Tissue lipid deposition is common in hyperlipidemic syndromes. Osseous xanthomatosis however, has not been reported in uncomplicated "essential hyperlipemia," although osseous involvement is characteristic of certain normocholesterolemic lipidoses. Two case reports of osseous xanthomatosis accompanying hypercholesterolemia and hyperglyceridemia have appeared. The first (Koch and Lewis) had certain features of eosinophilic granuloma of bone, while the second (Sørensen) resembles the case described below. Neither previous case report included pathological fractures complicating the osseous xanthomatosis.

The subject is a 64-year-old woman with hyperlipemia and cutaneous xanthomas for many years. Severe generalized atherosclerosis was noted. Fasting glucose levels were normal; glucose tolerance was impaired. A low-carbohydrate, high-fat diet diminished serum cholesterol levels from 1,100 to 1,400 to 500 to 600 mg% and triglyceride levels from 2,000 to 2,500 to 500 to 800 mg%. During the past year, pathological fractures of the right humerus and femur occurred at the site of osteolytic lesions. Similar lesions were also present in the left humerus and femur. Bone biopsy revealed cholesterol clefts and foam cells resembling xanthomatosis. Chlorophenoxyisobutyrate (CPIB), 2 g daily, lowered lipid levels, maintaining cholesterol in the 350 to 450 mg% range, triglycerides in the 400 to 500 mg% range. Attempts to diminish net bone resorption by gonadal steroid administration (while CPIB was continued) increased serum lipid levels when methyltestosterone was administered, but not when estrogen was administered.

Hypercholesterolemia and hyperglyceridemia of many years' duration would appear to be the primary factor in development of bone lesions, with osteoporosis an important contributory factor.

Qualitative and Quantitative Lipid Correlation in Experimental Endogenous Hyperlipemia

Antanas Butkus, Abel L. Robertson, Jr., and Irvine H. Page, Cleveland, Ohio

In clinical hyperlipemia a change takes place not only in serum lipid levels but also in their fatty acid composition; saturated and monounsaturated tend to replace polyunsaturates. The same trend is described both in arterial fatty streaks and human or experimental atherosclerosis.

Endogenous hyperlipemia in dogs that received Triton WR-1339 intravenously was used as a means of studying this relationship further. With progressive increase in plasma lipids, there was a concurrent increase in saturated fatty acids and decrease in polyunsaturated ones during a four-month study period. In severe hyperlipemia, oleic acid constituted almost half of the fatty acids, but only 24% in moderate hyperlipemia, and 22% in normal dogs; the corresponding figures for linoleic were 22, 45 and 45% respectively. This study of artificially elicited endogenous hyperlipemia suggests an association between severity of endogenous serum lipid elevations and fatty acid composition that resembles the patterns found in clinical hyperlipemia.

Evaluation of Episodic Atherosclerotic Lesions in Human Coronary Arteries (P)

Joseph Choi, Robert H. More, M. Daria Haust, and John C. Wyllie, Kingston, Ontario, Canada

Atherosclerosis progresses by the development of *de novo* lesions as well as by the increase in size of the individual lesions. This progress and growth may be the result of repeated episodes of deposition of various blood constituents on or in the vessel wall. In the coronary arteries, the growth of the individual lesions is the most important factor contributing to myocardial ischemia. In order to analyse the atherosclerotic lesions with respect to the nature and number of episodic layers comprising a given lesion, blocks of tissues from all main branches of coronary arteries removed at 14 standard sites from 100 human hearts obtained at autopsy, were examined microscopically. Of the 1,455 blocks removed, 1,025 contained lesions. Of the total 88 purely fatty lesions, 62 were found in the left and 36 in the right coronary artery. It was, however, difficult to assess whether the purely fatty lesions were the result of a single or multiple episodes. Of the 457 mixed fibro-fatty lesions, 319 were the outcome of a single episode, 99 of two and 33 of three episodes; four and five episodes were in "operation" twice each. Of the 366 "pure" fibrous plaques found, 260 were the outcome of a single, 75 of two, and 26 of three episodes. Four episodes were found in five instances. Pure insudation was seen in 44 lesions. Of the 32 large unorganized mural thrombi, one episode was found 24 times, two episodes seven times and three episodes in one instance. Microthrombi were

seen on 29 occasions. The distribution and prevalent location of all these lesions will be discussed in detail.

Effect of Estrogens on Serum and Bile Lipids in the Cockerel

Gregory B. Clarke, Savitri Jain, and Ruth Pick, Chicago, Illinois

Previous work has shown that estrogens raise serum cholesterol but produce an even greater rise in serum phospholipids so that the C/P ratio in the blood declines. These estrogens prevent coronary atherosclerosis produced by feeding cockerels high cholesterol-oil diets. In the present study, the effect of estrogen on lipid metabolism was analyzed further. Conjugated equine estrogens were administered at levels varying from 12.5 to 75 mg/day for five weeks to chickens receiving a 1% cholesterol- and 5% oil-supplemented diet. Bile, serum, and liver samples were obtained when the birds were killed. The bile cholesterol levels showed a diphasic dose-dependent response with an elevation in birds receiving the lowest dosage and a steady decrease in the level of bile cholesterol with increasing doses of Premarin. Liver cholesterol levels showed similar patterns. The bile acid levels of these birds showed a diphasic dose-dependent response, but the response was the reverse of that found in the bile cholesterol levels. The estrogens also modified the serum fatty acid pattern with a significant decrease in linoleic acid content in all groups receiving the hormone. Estrogens thus appear to modify many aspects of lipid metabolism. Especially significant is the effect on the essential fatty acid, linoleic acid.

Biological Interactions Among Nutritional Factors Related to Atherosclerosis

Thomas B. Clarkson and Hugh B. Lofland, Jr., Winston-Salem, North Carolina

Biological interactions among dietary variables, i.e., when an ingredient exerts one influence in a given situation and another in a different situation, have largely been overlooked in atherosclerosis research. When interactions exist or have not been shown to be absent, it is erroneous to assign its effect on atherosclerosis on the basis of simple effects alone.

Young White Carneau pigeons of both sexes were grouped, using a $4 \times 2 \times 2$ factorial design, and fed four types of dietary fat (30% of calories) and two types of dietary protein (casein-lactalbumin mixture 85% : 15%, or wheat gluten) at levels of either 8% or 30% of calories for 15 months. The four fats were unsupplemented margarine, butter, corn oil plus 0.3% cholesterol, and Crisco plus 0.3% cholesterol.

Both fat and protein had main effects on serum cholesterol levels; however, such effects become essentially meaningless in the presence of significant interactions. For example, corn oil plus cholesterol elevated levels of serum cholesterol, but only when fed with low levels of wheat gluten. Low levels of casein produced the opposite effect. Crisco plus cholesterol produced low levels of serum cholesterol when fed with low wheat gluten but high levels when fed with low casein. The presence of small amounts of cholesterol in some of the fats increased both the prevalence and extent of aortic atherosclerosis and was affected by the level and type of protein, type of fat, and sex of the bird. These data confirm the importance of biological interactions in studies of atherosclerosis.

Evidence of Alpha-1 Lipoprotein Polymorphism (P)

Louis Cohen and Juliana Djordjevich, Chicago, Illinois

A method has been developed using starch gel electrophoresis, which permits the separation and staining of the multiple bands which were found to comprise the alpha-1 lipoproteins in human whole serum. With this method serum samples from 210 males and 105 females have been studied. Three different patterns of bands have been distinguished, migrating in the post albumin region; they are called alpha-1-S, alpha-1-M, and alpha-1-F lipoproteins. Alpha-1-S has five bands, which stain strongly (S) with oil red 0; alpha-1-M has a similar pattern, but the staining intensity is moderate (M); and alpha-1-F has four bands, and is the faintest staining of the three types. These three patterns are reproducible with rare exception, when the same person is studied repeatedly over a period of several weeks. The frequencies of the alpha-1-S, alpha-1-M, and alpha-1-F forms were respectively 17.1, 57.2, and 25.7% in the males; and 58.3, 39.8, and 1.9%, in the females.

The study of lipoproteins of density 1.063 to 1.21, isolated by flotational ultracentrifugation, from sera showing each of the three forms, provided additional evidence of the polymorphism of alpha-1 lipoproteins. Such lipoproteins, intact or partially delipidated, maintained characteristic patterns, when studied electrophoretically in starch gels enriched with 8M urea or 8M urea and 2β mercaptoethanol.

These data suggest that human serum alpha-1 lipoproteins exist in more than one form. It remains to be established that there are chemical differences among the three types, and that this

polymorphism is metabolically or genetically significant.

Phylogenetic Aspects of the Cause of Human Atherosclerotic Disease

William S. Collens and Gerald B. Dobkin, Brooklyn, New York

The history of primate evolution appears to indicate that early man was an herbivorous animal. While soft tissues disintegrate and disappear rapidly after death, the bony structures of fossil skulls have been found to remain intact. A study of their dentition provides a fine point of reference from which may be deduced the dietary habits of these creatures.

The dental structures of herbivorous animals consist of sharp cutting incisors, while the molars have a flat or nodular surface used for crushing and grinding food. This presupposes that such animals are phylogenetically constructed to live on vegetables, leaves, roots, fruits, nuts and berries. On the other hand, the carnivore has a dental structure designed to provide him with the means of eating raw flesh. The canines are elongated, strong, and sharp-pointed. They are used for grasping and tearing flesh. The molars have a lateral edge which is sharp and in approximating the jaws are used for slicing flesh.

Examination of the dental structure of modern man reveals that he possesses all of the features of a strictly herbivorous animal. While designed to subsist on vegetarian foods, he has perverted his dietary habits to accept the food of the carnivore. It is postulated that man cannot handle carnivorous food like the carnivore. Herein may lie the basis for the high incidence of human atherosclerotic disease.

Experimental studies in the rabbit and dog are presented to show that the capability to handle carnivorous food is under the control of a homeostatic mechanism better developed in the carnivore than the herbivore.

Sodium Dextrothyroxine ($NaDT_4$) as a Cholesterolpenic Agent

Elmer E. Cooper, San Antonio, Texas

The thyroid analogue $NaDT_4$ (sodium dextrothyroxine) reduces cholesterol by the acceleration of its catabolism in the liver, with its subsequent excretion into the intestine via the biliary tract. The cholesterolpenic effect occurs in the diabetic, hypercholesterolemic, euthyroid and hypothyroid with approximately one-twentieth of the calorigenic effect of levothyroid preparations.

$NaDT_4$ in doses of 2 to 8 mg% per day were studied in 91 subjects followed from six to 48 months. The average control cholesterol was determined from three separate tests at weekly intervals. Follow-ups were made every two weeks by Bloor colorimetric method. There were no dietary restrictions.

Eighty-five of the 91 subjects had an appreciable reduction in serum cholesterol ranging from 28 to 132 mg%, with a mean maximum decrease of 66.3 mg%. During the study, there was no escape from cholesterolpenic effect. Actually, responses increased with duration of therapy. After four weeks, the fall was 14.3%, after 52 weeks 18.1%, at 108 weeks 19.9%, and over 150 weeks 25.5%.

Of the 91 subjects, seven reported side effects and discontinued the program: one because of nervousness, one because of thinning of the hair, two because of bleeding while on fixed doses of anticoagulants ($NaDT_4$ potentiates the anticoagulant effect on one-stage prothrombin time), and three of the eight angina patients because of increased severity and frequency of attacks.

There were no serious toxic effects encountered in hematopoietic, cardiovascular, renal, or hepatic systems.

Lipoprotein Electrophoretic Patterns in Diabetic Patients

Rawser P. Crank, Jr., Janet E. Fetner, George C. Klein, Atlanta, Georgia, Edwin C. Boyle, Charleston, South Carolina, and Gerald R. Cooper, Atlanta, Georgia

A modified method for lipoprotein electrophoresis was used to follow postabsorptive serum lipid changes in 29 diabetic patients with exudative retinopathy. Fifteen patients receiving 1.5 to 3 g nicotinic acid-aluminum nicotinate mixture were compared with 14 control patients on placebo in a clinical trial of the effect of the drug on diabetic retinal exudates.

Apparent changes in lipoprotein electrophoretic pattern phenotypes occurred within a six-month observation period in several patients in both drug and placebo groups. These changes occur in the electrophoretic pre-beta fraction. Evidently, they are associated with variation in cholesterol content of the preparative ultracentrifugal $beta_2$ fraction.

This lability in apparent electrophoretic lipoprotein phenotype in diabetic individuals was not obviously associated with nicotinic acid therapy. The system of lipoprotein phenotyping proposed by Frederickson and Lees may require some modification in the case of diabetic individuals.

No correlation of lipoprotein pattern was apparent, in these controlled diabetic patients, with severity of diabetes or degree of retinopathy observed.

The lipoprotein electrophoretic pattern shows

an extreme decrease in alpha-lipoprotein and loss of beta-lipoprotein definition in diabetic patients observed while out of control with severe lipemia.

Effect of Methyltestosterone on the Protein Moiety of Canine Serum α-Lipoproteins (P)

Quincy E. Crider, Reagan H. Bradford, and Robert H. Furman, Oklahoma City, Oklahoma

Methyltestosterone administration decreases canine serum cholesterol, triglycerides, and phospholipids without altering liver lipid concentrations, has a hypocholesterolemic effect in rats and reduces serum lipid levels in hyperlipemic subjects.

The specific and total radioactivities incorporated into serum free cholesterol in dogs administered C^{14}-acetate were decreased substantially during methyltestosterone treatment. We have extended this study to evaluate the effect of methyltestosterone on the incorporation of radioactivity into the protein moiety of serum α-lipoproteins ($D > 1.063$ g/ml) in dogs given C^{14}-lysine. The α-lipoprotein fraction accounts for approximately 75% of the serum total cholesterol in the dog.

Four mature dogs maintained on a routine laboratory diet containing 25% protein were injected intravenously with 200 μc of DL-5-C^{14}-lysine. Blood samples were obtained at intervals up to 11 hours after isotope injection. The α-lipoprotein fraction was isolated and freed of contaminating protein by ultracentrifugation. After the lipid was extracted, the radioactivity and nitrogen content of the protein moiety were determined. A second incorporation study was performed during methyltestosterone treatment (200 mg/day).

Methyltestosterone diminished serum lipid and α-lipoprotein lipid levels. The concentration of serum α-lipoprotein protein was markedly decreased and its specific radioactivity was reduced to approximately one-half the control value. The latter observations may account in part for the striking reduction in serum lipids associated with methyltestosterone administration.

Specific Serum Beta-Glucuronidase Activity and Susceptibility to Atherosclerosis in Various Species

P. William Curreri, Frances P. Keyes, and Benjamin F. Miller, Philadelphia, Pennsylvania

A specific method for determination of activity of beta-glucuronidase in serum has been devised by W. H. Fishman. The new method reduces interference by endogenous inhibitors and gives considerably higher values than his previous standard procedure. The enzyme activity has been determined in species susceptible to atherosclerosis and compared with others resistant to the disease.

Nineteen adult humans and ten adult swine of both sexes were studied as representatives of species suspectible to atherosclerosis; and ten adult dogs and six adult Sprague-Dawley rats as members of species resistant to atherosclerosis. Beta-glucuronidase activity was assayed in 0.2 ml serum at 37 C employing 0.006M phenolphthalein-glucuronide substrate in acetate buffer, pH 4.6. Results are expressed as micrograms of phenolphthalein released per 100 ml serum.

Beta-glucuronidase activity averaged 1,180 (range, 500 to 1,940 in the human; zero in each of the swine; 2,980 (range, 2,310 to 3,880) in the dog; and 6,740 (range, 5,190 to 8,250) in the rat. In the swine, the surprising finding of zero values was corroborated by the absence of activity in sera dialyzed to remove endogenous inhibitors. Also beta-glucuronidase when added to swine serum exhibited the expected activity.

It appears that the specific assay of serum beta-glucuronidase activity gives low values for susceptible species and high values for resistant ones, thereby supporting the results obtained in this laboratory on nine species by the non-specific method.

Procoagulant Effects of X-Ray Opaque Media

Herbert L. Davis and Lawrence R. James, Omaha, Nebraska

Several popular iodinated contrast media demonstrate significant procoagulant effects, suggesting that transient hypercoagulability may be a significant factor in the reactions to them. These effects include: (a) lowering blood clotting times in human beings after standard radiological injections of diatrizoate; (b) comparable lowering of clot times in dogs after injections of diatrizoate, iothalamate, iodopyracet, or acetrizoate; (c) reduction of blood loss from dogs after a standard Dermatome wound; (d) lowering of the recalcification times of human ACD plasmas; and (e) lowering of the gel times of relevant fibrinogen plus thrombin systems. Blood samples were secured through an indwelling plastic Angiocath catheter, maintained with saline drip to prevent clotting, and providing constant clot times of spaced samples in the absence of treatment. Injection of clinical doses of each of these reagents produced minimal clot times ten to 30 minutes later, with return to normal clot times 45 to 60 minutes after the infusion. Minimal clot times range 16 to 50% below the control values.

The two in vitro tests demonstrate that injection of the clinical doses of these media results

in moderate elevation of clot times, followed in about 20 minutes by minimal clot times associated with a remainder of about 5% of this dose, which is then soon completely cleared. This hypercoagulable state, correlated with the low concentration of medium, can be produced promptly by continuous injection of the dye, and can be promptly normalized by substituting saline injection. Heparin promises to be a useful prophylactic and therapeutic drug. In patients with atherosclerotic or stress hypercoagulability, these tendencies to thromboembolic episodes may not be readily or completely reversible, and may account for ischemic areas of heart, brain, kidney, lungs, etc.

Phospholipid Synthesis by Macrophages and Its Stimulation by Cholesterol (P)

Allan J. Day and Noel H. Fidge, Adelaide, South Australia

Macrophages obtained from the peritoneal cavity of rabbits were incubated in vitro with P^{32}-labeled phosphate in order to investigate the synthesis of phospholipid by these cells. After six hours' incubation, 0.25% of the P^{32}-labeled phosphate added to the medium had been converted to phospholipid in the cells. Fractionation of the labeled phospholipid on silicic acid-impregnated paper demonstrated that most of the label had been incorporated into lecithin (77.9% of the total at 6 hr) and into sphingomyelin (10.6% of the total at 6 hr), but some incorporation into phosphatidyl ethanolamine, inositol phosphatide, and probably phosphatidic acid also occurred.

Cholesterol particles (1μ diam) added to the medium to give a final concentration of either 0.25 or 0.625 mg/ml were taken up by the macrophages and shown to increase the incorporation of P^{32}-labeled phosphate into phospholipid by 30 to 40%. This increase in phospholipid synthesis was not accompanied by any increase in oxygen uptake, so it was concluded that the stimulation of phospholipid synthesis was not due to phagocytosis of the cholesterol particles. Fractionation of the labeled phospholipid synthesized following cholesterol uptake by the macrophages demonstrated that the increased incorporation was not due to specific increase in any particular fraction.

In view of the significant synthesis of phospholipid by macrophages and its stimulation following uptake of cholesterol, it is suggested that the synthesis of phospholipid known to occur in the arterial wall in atheroma is brought about by the macrophages present in the lesion.

Changes in Adipose Tissue Composition in Humans During Prolonged Feeding of Unsaturated Fat (P)

Seymour Dayton, Sam Hashimoto, and Morton L. Pearce, Los Angeles, California

Subcutaneous fat was obtained from men on a diet high in unsaturated fat (linoleic acid content: 38% of total fatty acid), and from control subjects. Adipose tissue linoleic acid content rose progressively in the experimental group, from 11% at start of study to 32% at five years. For subjects with mean adherence of 92% (based on meal attendance records), computed function describing the change in depot fat composition is $\log (35.6 - L) = 1.38 - 4.43 \times 10^{-4}\ t$, in which L is percentage of linoleic acid in adipose tissue fatty acid and t = time in days. The constant 35.6 is the computed asymptote. Half-time is 675 days.

Considerable variation in rate of rise of adipose tissue linoleic acid was observed. Differences in adherence rates, over the range 44 to 93%, accounted for little of this. Chief determinants of the change in linoleic acid concentration were body weight and changes in body weight. Stepwise multiple regression analysis yielded the function $\Delta L = -0.113\ W + 0.276\ \Delta W + 0.066\ A + 22.1$, in which ΔL = rise in depot fat linoleic acid concentration in the first year, as per cent of total fatty acid, W = initial body weight in pounds, ΔW = change in body weight in the first year, A = adherence in per cent. (Independent variables are given in order of declining individual correlation coefficients; multiple $r = 0.73$.) It is apparent that, in a study in which body weight is not rigorously controlled, adipose tissue sampling is not an adequate means of monitoring adherence.

Implications of the Linoleic Acid Concentrations of Atheroma Lipid Fractions

Seymour Dayton, Sam Hashimoto, and Morton L. Pearce, Los Angeles, California

Analysis of fatty acid composition was carried out on human atheroma, and on serum obtained from the same subjects within the last four months of life. Subjects were men on a conventional diet (control) and others on a diet high in unsaturated fat (experimental). In uncomplicated aortic atheroma, ratios of cholesterol ester linoleic acid concentrations to concentrations in the corresponding serum fraction were: control, 0.86 ± 0.09 (mean $\pm$ standard deviation); experimental, 0.63 ± 0.16 ($P < 0.01$). For triglyceride, corresponding ratios were: control, 1.06 ± 0.27; experimental, 0.61 ± 0.07 ($P < 0.001$). For phosphatide, ratios were: control, 0.58 ± 0.10; experimental, 0.52 ± 0.12 ($P > 0.3$).

Fatty acid synthesis occurs in atheroma but human tissues do not synthesize linoleic acid. This suggests that synthesis of other fatty acids within the atheroma may dilute the fatty acids of cholesterol ester and triglyceride taken up from plasma, and thus lower the linoleic acid concentrations of these atheroma components. It is postulated that the ratio cited may constitute an estimate of the fraction of fatty acid contributed by plasma to atheroma cholesterol and triglyceride. (Phosphatide is so heterogeneous that such a supposition would not be valid for this fraction.) Mean ratios for arachidonic acid are similar, tending to exclude peroxidation within the atheroma as a major mechanism of linoleic acid depletion.

The ratios cited for uncomplicated aortic atheroma of control subjects were significantly higher than those observed for coronary atheroma and complicated aortic atheroma of the same subjects, except for triglyceride of complicated aortic atheroma.

Familial Aggregations of Factors Associated with Coronary Heart Disease (P)

Sigismond Deutscher, Frederick H. Epstein, and Marcus O. Kjelsberg, Ann Arbor, Michigan

Serum cholesterol, systolic blood pressure (SBP), relative weight, and blood glucose after a standard load are associated with coronary heart disease. Because of familial predisposition in this disorder, a quantitative assessment was made of relations between parents and children and within sibships regarding these risk factors. Relatively high levels might be controlled early in life.

These four variables were measured in approximately 6,000 persons (Tecumseh Community Health Study). For each variable, participants were classified as follows: high (above the eightieth age-sex specific percentile point), low (lowest quintile), and intermediate (three middle quintiles).

Results for serum cholesterol: with both parents high, 44% (25/57) of young children (below age 15) and 48% (12/25) of older children (including adults) were also high. With one parent high and one low, proportions of high for the young and older children were 18% (15/82) and 15% (8/53), respectively. With both parents low, only 6% (5/86, 2/35) of children in either age group were high.

For SBP, percentages of children high were 33% (27/83) and 40% (17/42) with both parents high; 23% (46/196) and 19% (10/52) with one parent high and one low; and 11% (15/136) and 3% (1/32) with both parents low.

Similar patterns were observed for the remaining two variables; findings were corroborated for all four factors by sibship analysis.

Conclusion: Early in life as well as during adulthood, children of parents with high levels of these factors have an increased probability of presenting such levels themselves.

Effect of Chlorophenoxyisobutyrate (CPIB) on Serum and Tissue Triglyceride (P)

Charles H. Duncan and Maurice M. Best, Louisville, Kentucky

We have previously reported that CPIB effects a reduction of serum triglyceride in the rat, and that the net output of triglyceride from the isolated perfused liver of the rat fed CPIB is significantly reduced. To further study this phenomenon, the influence of CPIB on the hyperlipemia produced by Triton was investigated. Triton, 400 mg/kg body weight, was injected intravenously into control rats and into rats fed 0.25% CPIB for two weeks, and groups of animals killed at two, four, and six hours. Serum triglycerides in the control rats were 88, 394, 620 and 710 mg/100 ml at zero, two, four and six hours respectively. In the CPIB-fed animals, serum triglycerides were 33, 280, 453, and 615 mg/100 ml. Thus, although CPIB effected a significant reduction ($P < .001$) in baseline fasting serum triglyceride, its effect on Triton-induced hyperlipemia was equivocal. To explore possible effects of CPIB on tissue lipids, the concentrations of cholesterol and of triglyceride in the kidneys of the above animals were determined. Kidney total cholesterol in control and CPIB groups was 4.05 and 4.01 mg/g respectively. Kidney triglyceride was $4.07 \pm .48$ mg/g in the control group, and $2.52 \pm .40$ in the CPIB group. It thus appears that CPIB effects a significant reduction not only in serum triglyceride but also in the triglyceride concentration of at least one tissue, the kidney ($P < .001$).

AY 9944, an Inhibitor of Cholesterol Biosynthesis, as Tool in the Estimation of the Rate of Cholesterogenesis

Dushan Dvornik, Morris L. Givner, and Jean Guy Rochefort, Montreal, Quebec, Canada

AY 9944 (trans-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride) has been shown to inhibit the biosynthesis of cholesterol by arresting the enzymatic conversion of the intermediate 7-dehydrocholesterol to cholesterol. As expected, following oral administration of AY 9944, 7-dehydrocholesterol ($\Delta^{5,7}$) is found in the serum and tissues of laboratory animals, thus indicating that, in the presence of the agent, $\Delta^{5,7}$ is biosynthesized instead of cholesterol (Δ^{5}). It seems likely that the rate of $\Delta^{5,7}$ formation corresponds to the rate of cholesterogenesis before AY 9944

administration. Since $\Delta^{5,7}$ is normally not found in the blood of laboratory animals and humans, the amount of $\Delta^{5,7}$ detected after a certain period of time, following treatment with the inhibitor should correspond to the amount of Δ^5 which the untreated organism would synthesize during the same period of time.

In order to test the possibility of using AY 9944 as tool to estimate the rate of endogenous cholesterol formation, male albino rats (ten per group) were given one single oral dose of 4.64 mg/kg (10 μmole/kg) of AY 9944 and, 24 hours later, the levels of $\Delta^{5,7}$ and Δ^5 were determined in the serum. In preliminary experiments the age-dependent rate of cholesterogenesis was reflected in the serum $\Delta^{5,7}$ level: eight-week-old rats (average wt, 278 g) had $\Delta^{5,7}$, 3.5 mg% and Δ^5, 46 mg%; in 25-day-old rats (average wt, 54 g) $\Delta^{5,7}$ was 7.7 mg% and Δ^5, 48 mg%, respectively.

In view of its capacity to produce, instead of cholesterol, the readily detectable 7-dehydrocholesterol, AY 9944 may be a useful laboratory tool for the estimation of the rate of endogenous cholesterol formation.

Effect of Highly Unsaturated Fats Upon the Rate of Lipolysis of Fasting Triglycerides via Lipoprotein Lipase

Hyman Engelberg, Beverly Hills, California

The mechanism whereby unsaturated fats lower serum triglycerides is unknown. This study investigates the possibility that postabsorptive low-density lipoproteins might vary, with dietary changes, as a substrate for triglyceride lipolysis via lipoprotein lipase. There is evidence that this enzyme functions in the removal of endogenously synthesized triglycerides from the bloodstream.

Studies were completed in 49 individuals. The diet was unchanged except for the addition of highly unsaturated fish oils which were taken for several weeks. Blood was drawn for lipid determinations and the special enzymatic studies prior to the oil ingestion, at the end of the experimental period, and several months later in many instances. The rate of triglyceride lipolysis was determined as follows: postheparin plasma was obtained from one donor with minimal fasting serum triglycerides. The subject's plasma, with albumin added, was incubated with postheparin plasma and the release of free fatty acids measured every ten minutes for 30 minutes.

The results were: fasting triglycerides decreased over 20% in 20 individuals; the average rate of lipolysis increased 0.44 mEq/L/hr, although there was less substrate available. In 20 cases triglycerides were unchanged; the rate of lipolysis increased 0.08 mEq/L/hr. In nine instances triglycerides increased; the rate of lipolysis increased 0.05 mEq/L/hr. The findings indicate that when triglycerides are lowered by unsaturated fats the endogenously synthesized lipoproteins are a better substrate for lipolysis via lipoprotein lipase. This affords a logical mechanism for the triglyceride reduction.

Effect of Scarring of the Wall on the Thrombosis of Human Blood in Vitro

Hyman Engelberg and Herbert Tanney, Beverly Hills, California

Chandler has described a method for the production of a true platelet-head thrombus in vitro using human blood. Recalcified whole blood is placed in a rotating plastic loop, and the interval between the initiation of rotation and the endpoint of thrombus formation is determined The procedure results in an arterial-type thrombus rather than a clot, an important distinction in studies of thrombosis.

Studies have been performed on blood aliquots in 50 subjects in whom the thrombosis time was compared, using smooth and mechanically scratched plastic tubing. In 75% the thrombosis time was shortened in the scarred tubing. The results are statistically significant, the average decrease being more than three times the standard deviation of the method (0.45 minutes). Similar decreases using scarred tubing were obtained when platelet-rich plasma was used rather than whole blood.

The results indicate that roughening of the vascular wall per se, without the intervention of tissue thromboplastin, accelerates the tendency of blood to thrombose. Furthermore, the data of the plasma experiments suggest that this effect does not occur via the enhancement of platelet agglutination resulting from the release of adenosine diphosphate from injured erythrocytes.

Comparative Effects of Guar Gum and Pectin on Human Serum Cholesterol Levels

Marvin J. Fahrenbach, Benjamin A. Riccardi, Pearl River, New York, John C. Saunders, Irwin N. Lourie, Orangeburg, New York, and John G. Heider, Pearl River, New York

Serum cholesterol levels were determined at two-week intervals over a two-month period in 70 male patients, aged 18 to 60 years, in a mental institution. Following this pretreatment period, the subjects were randomly distributed into three approximately equal groups according to ward location, serum cholesterol, and body weight. One group (I) served as an untreated control; the other two groups received a preswelled solid formulation of either guar gum (II) or pectin (III) in three divided doses before meals. Aver-

age pretreatment cholesterol levels of these groups were 233, 223 and 222 mg %, respectively. During a subsequent period of 66 days when the two treated groups received 6 g daily of guar gum or pectin, there was a statistically significant reduction of 12 mg % from the control in group II, but no reduction in group III. The daily dose was then increased to 12 g for the next 52 days, which resulted in a statistically significant reduction from the control of 14 mg % in group II, but again no reduction in group III.

Two groups of 25 subjects with moderately elevated serum cholesterol (average value, 268 mg %) were selected from the previous test subjects; one group served as an untreated control (IV), and the other group (V) received 12 g guar gum for 45 days, and finally 18 g of guar gum for an additional 14 days. During the treatment period, there was a highly significant average reduction in group V of 30 mg%, and during the last period of 14 days, the reduction was 41 mg %.

Effects of Hypocholesteremic Drugs on the Incorporation of C^{14}-labeled Tripalmitin into Lipoproteins

Leonard J. Feinberg, Herschel Sandberg, Etienne Van der Stichele, Howard Warner, and Samuel Bellet, Philadelphia, Pennsylvania

Since ethyl α-p-chlorophenoxyisobutyrate (CPIB) has been reported to lower the serum triglyceride levels of hyperlipemic subjects and since both CPIB and D-thyroxine appear to lower the serum cholesterol levels of hypercholesteremic individuals, it was decided to study the effects of these agents on triglyceride transport in the following manner: Tripalmitin-C^{14} was administered orally to nine hypercholesteremic subjects. Serial blood samples (two, four, six, eight, and 24 hours later) were analyzed for radioactivity. The total lipids were then extracted and assayed for C^{14}. The plasmas were fractionated in a preparative ultracentrifuge. Lipoprotein fractions with specific gravity < 1.006 and those with specific gravity > 1.063 were obtained and analyzed for β activity. Fasting blood samples were analyzed for serum triglyceride, cholesterol, and phospholipid concentration.

Seven of the patients were then treated with CPIB and two were treated with D-thyroxine for three to six weeks. Studies similar to those described above were then performed. Both subjects treated with D-thyroxine, and five of the seven patients treated with CPIB, showed a significant decrease in the radioactivity found in the blood, particularly the very low-density lipoprotein fraction (specific gravity < 1.006). A concomitant lowering of the serum cholesterol and triglyceride concentration, but not the phospholipid concentration, was noted in the patients on CPIB. It was therefore felt that the drugs appeared to inhibit the incorporation of C^{14}-labeled triglyceride into the very low-density lipoproteins of hypercholesteremic subjects.

Changes With Aging of Some Structural Aortic Connective Tissue Proteins

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Studies on the insoluble structural connective tissue components of aortic wall have been carried out to determine what changes may occur with aging. Extraction with hot alkaline solutions was used to isolate elastin from powdered, defatted, crude connective tissue (CCT) from tunica intima and media of subjects ranging in age from four months to 80 years. Other samples of the same CCT were treated with highly purified collagenase (Cl. histolyticum) to remove collagen, and then subjected to digestion by bovine pancreatic elastase. The insoluble protein(s) remaining after repeated collagenase digestion of CCT was different from elastin in amino acid composition, particularly in older subjects, and contained sialic acid, hexose, and fucose, but no uronic acids. The same residues contained glycoprotein(s), elastin, and, in tissues from older subjects, a collagenase-resistant protein which resembles collagen in amino acid composition. Pancreatic elastase with a broad specificity for substrates other than elastin also hydrolyzed the glycoprotein(s).

The following changes with age were found in aortic CCT: (1) Elastin content decreases. (2) The aspartic acid and histidine content of elastin increases markedly. Slight increases in glutamic acid and arginine content were noted. (3) A marked increase in insoluble glycoprotein occurs sometime between the age of seven and 22 years. (4) There was an increase in collagen resistant to collagenase digestion.

Objective Biochemical Evaluation of Dietary Adherence in the Young, Free-living Coronary Male

Alan I. Fleischman, Thomas Hayton, and Marvin L. Bierenbaum, Montclair, New Jersey

The usual procedure for determining adherence to controlled-fat diets in free-living individuals is by dietary recall, supplemented by qualitative evaluation of serum and tissue fatty acids. During long-term evaluation of the effects of controlled-fat diets, the necessity of quantitative measurements of dietary adherence is obvious. Thirty-nine free-living, ECG-proved coronary males, between the ages of 20 and 50 years, were

placed on one of two diets for periods up to four years. Both diets contained approximately 21% of calories as protein, 51% as carbohydrates, and 28% as fats. Total calories ranged between 1,500 and 2,900, all men maintaining ideal weight during the entire study. Diet I contained 14.1% of calories as polyenoic fats and 5.5% saturated fat; diet II contained 3.3% polyenoic fat and 9.6% saturated fat.

Serum triglycerides were isolated by thin-layer chromatography and the fatty acids determined by vapor-phase chromatography. Dietary linoleate, as per cent of calories, was determined from the regression equation: Log_{10}dietary linoleate $= 0.179 + 0.024$ (diene $-$ triene $+$ tetraene). For the 21 men on diet I, the mean determined dietary linoleate was 12.3% of calories, SD $= 4.3$, while for the 18 men on diet II, it was 3.4%, SD $= 1.6$, for both $P < 0.01$. These values compared closely with the values of 14.1% and 3.3% calculated from the two diets. This procedure provides an objective means of determining both the consistently good adherer and the degree of adherence of the moderate and poor adherer.

Influence of Experimentally Induced Atherosclerosis on the Sulfate Content of the Aortic Wall (P)

Donald T. Forman, Song Shik Choi, and C. Bruce Taylor, Evanston, Illinois

Turnover rates of aortic acid mucopolysaccharide sulfate were determined in control and cholesterol-fed rabbits receiving weekly doses of 25 μc of S^{35}. Animals were sacrificed sequentially and their aortae studied autoradiographically and radiochemically for total and organic radiosulfate. Atheromata from animals fed cholesterol up to 45 days showed little propensity for increased acid mucopolysaccharide sulfate deposition. Striking localization of radiosulfate was associated with atheromata from animals fed cholesterol 60 to 112 days.

Based upon radioactivity per g of tissue, radiochemical analyses revealed a significant increase in both total and organic sulfate in the aortae of animals fed cholesterol from 60 to 112 days, but there was a decrease, on a weight basis, in animals fed cholesterol up to 60 days. After 112 days on cholesterol, experimental animals had 1.7 times as much aortic total radiosulfate and 2.5 times as much organic radiosulfate as control aortae. These results suggest that the increased concentration of aortic radiosulfate may be due to a connective tissue reaction and ground substance change initiated by the lipid deposition.

Electrocardiographic and Pathological Study of Clinically Diagnosed Multiple Myocardial Infarctions

Stafford W. Gedge, Richard W. P. Achor, Kenneth G. Berge, and Jesse E. Edwards, Rochester, Minnesota

In coronary heart disease with healed myocardial infarcts, suspicion of recurrent infarction is a common clinical problem. The clinical and autopsy findings in 52 cases of clinically diagnosed multiple myocardial infarction were reviewed with regard to difficulties in electrocardiographic documentation of recurrent infarction. The cases selected afforded clinical data and electrocardiograms for each suspected recurrence. Clinical and autopsy findings were reviewed independently.

Two episodes of infarction were diagnosed clinically in 30 cases, three in 17 cases, and four in 5 cases. In those with two episodes, diagnostic electrocardiograms were associated with the first episode in 29 and with the second episode in 27. The electrocardiographic and autopsy findings correlated well in all except three initial and four second infarctions. Among the cases with three infarctions, all 17 had diagnostic electrocardiograms associated with the first two episodes but the third infarction was obscured electrocardiographically in two. In the group with four infarctions, the electrocardiograms were diagnostic during the first three episodes in all five cases, but were obscured following the fourth episode in two cases.

Eight of nine cases with ventricular aneurysm had elevations of the S-T segments of eight months' to ten years' duration. Conversely, 11 cases with persistent S-T segment elevations had no ventricular aneurysm.

These data demonstrate the value and limitations of the 12-lead electrocardiogram in the recognition of recurrent myocardial infarction.

Comparison of the Fine Structure of Human Aortic Intimal Fatty Streaks with Experimental Lesions in the Dog, Rabbit, and Baboon (P)

Jack C. Geer, New Orleans, Louisiana

This study compares the electron microscopic structure of aortic intimal fatty streaks from 46 humans (age two months to 37 years) with cholesterol-thiouracil-induced lesions in seven dogs and cholesterol-induced lesions in 12 rabbits and six baboons. In human and experimental lesions detectable only after gross staining for lipid, the lipid is predominantly in the form of electron-dense irregular particles in the interstitial tissue. Fatty streaks detectable without staining also demonstrate extracellular lipid and have in addition large numbers of lipid-containing cells—smooth muscle and foam cells. Foam cells are

derived from round cells, presumably blood monocytes in the tissue. Lipid accumulation in the agranular endoplasmic reticulum of smooth muscle and foam cells suggests that both cell types synthesize lipid. Foam cells also demonstrate intracellular lipid morphologically identical to that in the extra-cellular space, indicating phagocytosis. Smooth muscle and foam cells are the only cells in experimental lesions. A third cell type in the human intima has small arrays of filaments morphologically identical to myofilaments, and this cell is presumed to be an immature smooth muscle cell. Though there are differences in anatomic localization and gross and light microscopic appearance between the human and experimental lesions, the lesions in the electron microscope have substantially identical cellular and extracellular features. These observations indicate that any of these experimental animals are suitable for studying mechanisms of lipid accumulation in arterial lesions.

Effect of Chlorphenisate plus Androsterone on Elevated Serum Cholesterol and Triglyceride Levels

Maxwell L. Gelfand and Michael M. Garber, New York, New York

The association of elevated levels of blood cholesterol and triglycerides with an increase in the incidence of atherosclerosis is well established. A number of drugs have been employed to reduce these elevated blood lipid levels in order to diminish the incidence of ischemic heart disease. Recently, a new pharmacologic agent, chlorphenisate plus androsterone, has been tried by many observers in patients with elevated levels of serum cholesterol and triglycerides with significant success. The purpose of this investigation is to study the effect of the above-mentioned drug in patients with elevated cholesterol levels and to determine its long-term effect on the incidence of myocardial infarction.

A group of 12 patients, both males and females, whose ages varied from 39 to 65, were given 2 g of the drug orally in four divided doses. Two patients had xanthomatosis tuberosum, one had associated osteogenesis imperfecta, two had diabetes mellitus, three had severe angina, and six had previous episodes of myocardial infarction. These patients were studied for a period of nine months and seen regularly at a clinic where blood determinations for serum cholesterol, triglycerides, uric acid, total protein, blood count, and liver function studies were done at regular intervals.

Results: Most patients showed a significant lowering of the blood cholesterol and triglyceride levels. The blood uric acid and the total proteins were unaffected. Blood counts and liver function tests were normal. Nausea was experienced by several patients at the outset of therapy but subsequently cleared. The two patients with xanthomatosis tuberosum showed considerable improvement of the cutaneous lesions. Angina improved in two subjects, and in all there were no new episodes of myocardial infarction.

Relations between Circulating Blood and Atherogenesis (P)

I. Ernest Gonzalez, Edwin J. Wylie, San Francisco, California, and Freddy Vermeulen, Tilburg, Holland

During the past ten years, segments of atherosclerotic arteries have been replaced by tubular dacron, teflon and other synthetic prostheses. We have observed on numerous occasions that focal atheroma often form on the luminal surface of these synthetic prostheses. Morphological, histochemical and histoenzymatic studies indicate that these lesions are very similar to atheroma forming on the arterial wall. Since lesions forming on the synthetic prostheses do not appear to be outgrowths of the arterial wall, it occurred to us that these atheroma might possibly develop from constituents of the circulating blood.

To test this postulate, small knitted dacron ribbons were suspended in midaxial position within a thin-walled teflon tube. These tubes were subsequently inserted in the thoracic aorta of 40 rabbits and in the abdominal aorta of 16 hyperlipemic dogs. Five months after the tubes had been implanted, lesions began to form on the surface of the knitted dacron ribbons, but the wall of the smooth teflon tubing was completely free of lesions and blood constituents. Since the dacron ribbons were completely isolated from the arterial wall by the interposed teflon tube, we have concluded that the atheroma formed on the surface of the dacron ribbons organized from elements derived from the circulating blood.

Our studies suggest the prime factor in the development of these experimental lesions is the circulating blood and not the arterial wall. These findings might also be applicable to the organization of human atheroma.

Arterial Intimal Muscular Hyperplasia and Lipid Deposition in Dietary Atherosclerosis

Ira Gore and Max L. Goodman, Boston, Massachusetts

Intimal smooth muscle accumulation is considered an early event in atherogenesis which determines the localization of subsequent focal lipid deposits. Whether fatty lesions result from local cellular synthesis, or from permeation by a lipid-rich plasma ultrafiltrate, has not been estab-

lished. To explore this problem, arterial intimal muscular hyperplasia was produced in rabbits by temporary isolation of a segment of common carotid artery using resorbable suture (group 1), and hypervitaminosis D (group 2). After three weeks to allow development of intimal proliferation, cholesterol was added to the diet for periods ranging from six to ten weeks. Similarly prepared stock-fed animals served as controls. Additionally, cholesterol diet controls were provided by the contralateral carotid artery and the aorta in group 1.

Hypervitaminosis D produced extensive medial calcification and intimal muscular proliferation. Cholesterol feeding did not affect intimal cells directly overlying calcific plaques. By contrast, intimal cells at the plaque margins (group 2) and those which formed in the intima and lumen of the temporarily isolated carotid artery segments (group 1) were filled with lipid. The sparing of the intima overlying calcific plaques from lipid deposits seems attributable to interference with vascular permeability by the mineralized deposit.

Sites of Feedback Inhibition of Hepatic Cholesterol Biosynthesis (P)

R. Gordon Gould, Elizabeth A. Swyryd, and Lucy Suzuki, Palo Alto, California

It has been generally accepted that the reduction of β-hydroxy-β-methylglutaryl CoA (HMG-CoA) to mevalonate by HMGCoA reductase is the only site of feedback inhibition of cholesterol biosynthesis in liver. A re-investigation has disclosed other sites of inhibition, as measured by incubation of various labeled precursors with liver slices or homogenates and by in vivo studies in rats fed cholesterol for periods varying from one day to over a year. After one day of 1% cholesterol diet, incorporation of acetate-1-C^{14} into cholesterol in liver homogenate decreased to $<5\%$ of the control value and on continued feeding stayed at about the same level (0.1 to 5%). Mevalonate-2-C^{14} (MVA) incorporation was decreased to about 50% of its control value after one day, 20% after a week, and 10% after a month. After 100 to 400 days of cholesterol feeding, cholesterol synthesis from MVA was inhibited as much as from acetate, but conversion of squalene-C^{14} to cholesterol was not consistently inhibited at any time. Results with farnesylpyrophosphate-C^{14} (FPP) indicate a site of feedback inhibition at the conversion of FPP to squalene and one or more sites between MVA and FPP. The inhibition of MVA conversion to cholesterol has not been observed except when acetate inhibition was almost complete and hence is probably secondary to the inhibition of acetate. Efforts to demonstrate conversion of HMGCoA into sterols by normal rat liver homgenate were unsuccessful, supporting the recent suggestion of Brodie et al. that HMGCoA is not an intermediate in cholesterol synthesis. The primary control of feedback inhibition is before mevalonate, but the specific intermediate and enzyme are still not definitely identified.

Physiochemical Character of Blood and Experimental Intra-arterial Lesions

Marshall E. Groover, Jr. and Clarke Stout, Oklahoma City, Oklahoma

Placing a silk thread in the wall of an artery offers an opportunity to study factors governing the appearance of an experimental arterial lesion which begins as a thrombus and ultimately appears as an organized fat-containing plaque. In earlier studies, the size of experimental lesions has correlated inversely with the electrophoretic mobility of plasma lipoprotein and directly with the compressibility of the red cells as determined by fractional centrifugation. This study was directed at clarifying the mitigating effect of heparin on the lesion.

Twenty-seven rats, 27 rabbits, and nine baboons were studied. One group of each was given subcutaneously 1,000 units heparin/kg four hours or more prior to placing the thread. A second group was given 0.01 mg histamine phosphate, and a third group 0.5 ml physiological saline. Animals were sacrificed under pentobarbital anesthesia by the rapid intra-arterial injection of formalin, 30 minutes, three weeks, and six weeks after placing the thread. There was a striking correlation between the agents given, physical measurements in the blood, and the size of the initial clot and later arterial lesions. The heparin group showed consistently increased lipoprotein mobility and decreased red cell compressibility associated with very small lesions compared to the saline controls. Conversely, the histamine group displayed consistently shortened lipoprotein mobility, increased red cell compressibility with large red-cell-rich mural lesions. The data suggest that the size of experimentally induced arterial lesions may be dependent in part on physiochemical characteristics of the blood that can be manipulated.

Physiochemical Changes in Blood During Emotional Stress with Allergy and Angina Pectoris

Marshall E. Groover, Jr. and Clarke Stout, Oklahoma City, Oklahoma

The electrophoretic mobility of lipoprotein and the compressibility of red cells have been used as an indication of changes in the physiochemical state of blood associated with alterations in the

development of experimental intra-arterial thrombi. While the mechanism of thrombus formation is not completely understood, size and red cell content can be altered in many ways, augmented by histamine and mitigated by heparin. This study was designed to determine the clinical condition associated with changes in red cell compressibility and lipoprotein mobility in man.

Postmyocardial infarction patients and their matched controls were seen at four- to six-week intervals for clinical evaluation. Capillary blood was obtained in microhematocrit tubes, from which red cell compressibility was determined by fractional centrifugation and the supernatant plasma used for electrophoresis. Six patients were observed during periods of unusual emotional stress. They complained of substernal pain, allergic rhinitis or urticaria, and exhibited a decrease in "b" lipoprotein mobility varying from 8.0 to 14.0 mm, and an increase in the red cell compressibility from + 0.1% above the hematocrit corrected normal to as much as +0.9% above normal. The increased red cell compressibility was seen to accompany the decrease in electrophoretic mobility in these patients in striking resemblance to the changes produced by heparin and histamine in experimental animals and associated with alterations in the size and red cell content of intra-arterial lesions.

Effects of Ethynylestradiol and Norethynodrel Plus Ethynylestradiol 3-Methyl Ether on Serum Triglyceride Levels

Miasnig Hagopian and Roger W. Robinson, Worcester, Massachusetts

The effect of ethynylestradiol (EED) on the serum levels of total triglycerides has been investigated. Daily dose levels of 0.01, 0.02 and 0.1 mg of EED were administered orally to three groups of postmenopausal women consisting of 28 patients. Three serum triglyceride values were obtained for each subject, a pretreatment control, after one month of daily treatment with EED, and one month after termination of treatment.

The total triglycerides were isolated by thin-layer chromatography of a total lipid extract of serum. The triglyceride-containing zones were transferred quantitatively into test tubes, and the triglycerides determined directly, using an acid-dichromate total oxidation method similar to that reported by Amenta.

The results indicate that EED induces an elevation of serum triglyceride concentration. The mean differences of the combined dose levels were: pretreatment, 143 mg %; one month on EED, 170 mg %; and one month post-treatment, 161 mg %. The observed changes, presented in the same order, at each dose level were as follows: ten subjects at 0.01 mg EED, 124, 166, 163 mg %; eight subjects at 0.02 mg EED, 139, 144, 140 mg %; ten subjects at 0.1 mg EED, 165, 194 and 175 mg %.

In 25 women, who received 10 mg daily of a combination of norethynodrel plus ethynylestradiol 3-methyl ether, the mean control triglycerides were 112 mg %. On treatment for one month, the triglycerides rose to 149 mg %.

Atherosclerosis: Effect of Anti-inflammatory Steroids Prednisone and Dexamethasone

Denham Harman, Omaha, Nebraska

The inflammatory response of the arterial wall to injury appears to be involved in atherogenesis. Cortisone has previously been shown to inhibit cholesterol-induced rabbit atherosclerosis. This work has been extended now to prednisone and dexamethasone. Three groups of individually caged male New Zealand rabbits were given daily 100 g of rabbit chow containing 1% cholesterol; one group served as a control while the other two had a steroid added to the diet as a fine powder (prednisone, 0.5 mg or 1.0 mg/day/rabbit; dexamethasone, 0.075 mg or 0.15 mg or 0.15 mg/day/rabbit). The prednisone experiment was terminated after 37 days of feeding; blood was obtained for total serum cholesterol and the aorta graded, after staining with sudan red, in the arch and thoracic areas for atherosclerosis on a scale of 0 to 4+. The number of animals in each group, the average serum cholesterol level (mg/100 ml) and the average grading in the arch and thoracic areas for the three groups were: control (10, 2,855, 2.30, 1.43); 0.5 mg/day (10, 3,240, 1.83, 0.90); 1.0 mg/day (10, 3,590, 1.70, 0.45). Corresponding data for the dexamethasone experiment: control (9, 2,560, 1.96, 0.71); 0.075 mg/day (8, 3,730, 0.92, 0.11); 0.15 mg/day (5, 5,240, 0.55, 0.17). Thus, both prednisone and dexamethasone inhibit cholesterol-induced rabbit atherosclerosis even though they, like cortisone, elevate serum cholesterol levels. The atherosclerosis-inhibiting effect of these steroids is presently attributed to a depression of the inflammatory response of the arterial wall to deposited lipids.

Atherosclerosis and Aging: Effect of Dietary Fats

Denham Harman, Omaha, Nebraska

Polyunsaturated fats lower serum cholesterol levels and thus presumably decrease atherogenesis. The expected beneficial effect of increasing the dietary intake of polyunsaturates may be more than offset by deleterious changes resulting in part from increased tissue peroxidation and changes in membrane permeabilities. To evaluate this possibility, groups of C3H female mice (60

per group) were fed (isocalorically), starting shortly after weaning, semi-synthetic diets containing 5, 10, or 20% by weight of either lard, olive oil, corn oil, safflower oil, or distilled triglycerides of menhaden oil. The diets contained 20 mg Vitamin E/100 g; no peroxides have been found in stored diets. The mice, ear-coded, were weighed and counted each month. The per cent of the original group still alive in the 5, 10, and 20% diet groups respectively at 16 and 20 months of age were: *16 months*—lard (41.4, 31.1, 42.4), olive oil (43.1, 37.9, 37.7), corn oil (40.7, 31.6, 24.1), safflower oil (38.6, 23.7 22.8) menhaden oil (35.0, 29.8 ,18.6); *20 months*—lard (14.0, 10.7, 8.6), olive oil (19.0, 5.3, 1.7), corn oil (7.0, 6.9, 0.0), safflower oil (11.9, 3.4, 1.7), menhaden oil (6.8, 1.7, 5.3). The tumor incidence was essentially the same in all groups. Thus increasing both the amount of dietary fat and the degree of unsaturation increased the mortality rate. These data suggest that in man the real adverse effect of high fat diets, particularly those rich in polyunsaturates (even though they do lower serum cholesterol levels), may be a shortening of the life span, with atherosclerosis but one of a number of means by which this is achieved.

Quantification of Lipoprotein Fractions by Paper Electrophoresis (P)

Frederick T. Hatch, Pentti K. Reissell, and Lillian M. Hagopian, Boston, Massachusetts

A combination of differences in charge particle size, and interactions with the supporting medium permits fractionation of serum lipoproteins by paper electrophoresis. Addition of 1% albumin to barbital buffer (pH 8.6, ionic strength 0.1) gives improved resolution of very low density fractions. Five zones are visible on Oil Red 0-stained strips in decreasing order of mobility: α_1—high density; Pre-β—very low density; β—low density; "Trail"—very low density; Origin—chylomicrons.

The relationships among lipoprotein fractions and cholesterol and triglyceride levels of fasting serum have been studied in 40 men aged 23 to 49 years (20 healthy and 20 with coronary heart disease). Quantification of the electrophoretic patterns was by densitometry with automatic integration in the Spinco Analytrol. Multiple regression equations were calculated in the form: Lipoprotein fraction (Y) (integration units) $= a + b_{y1.2}$ [cholesterol (X_1) (mg %)] $+ b_{y2.1}$ [triglycerides (X_2) (mg %)].

Alpha$_1$-lipoprotein was not dependent on either cholesterol or triglyceride levels of whole serum. Pre-β-lipoprotein was dependent on both cholesterol and triglycerides. Beta-lipoprotein was dependent upon cholesterol only. "Trail" fraction was related to triglycerides only. Chylomicrons were absent in the fasting sera. The patients showed lower α_1- and higher β- and Pre-β lipoproteins than the controls. All demonstrated relationships were statistically significant.

The method permits approximately quantitative determination of the partition of transported lipids among the various lipoproteins. It is more suitable for hospital laboratories and epidemiological surveys than analytical ultracentrifugation.

Demonstration of Albumin in Human Atherosclerotic Lesions by the Fluorescent Antibody Technique

M. Daria Haust, Joseph Choi, John C. Wyllie, and Robert H. More, Kingston, Ontario, Canada

An antiserum against human serum albumin was produced in rabbits and characterized by immunoelectrophoresis. The antiserum contained antibodies against transferrin, alpha-1-lipoprotein and alpha-1-glycoprotein, in addition to albumin. Antitransferrin, anti-alpha-1-lipoprotein and anti-alpha-1-glycoprotein were removed by adsorption with appropriate fractions. The gamma globulin fraction of the antiserum was conjugated with fluorescein isothiocyanate. Fifty yellow streaks, 50 white plaques and 50 blocks of normal intima were obtained from human aortae at post mortem. Rapidly frozen blocks were sectioned in a cryostat. Sections were stained with the conjugate and appropriate control procedures were carried out. A semiquantitative method for albumin was adopted and the amount of the albumin in the sections was graded. In yellow streaks, albumin was demonstrated in large amounts in macrophages, while small amounts were observed in endothelial cells and in the extracellular space. In young white plaques, it was found largely in the extracellular space and frequently within cells. Mature white plaques did not contain albumin. Albumin was demonstrated in endothelial cells and in the extracellular space of normal intima but it was not as abundant as in some atherosclerotic lesions.

Effects of Aging on the Carotid Pulse

Robin E. Herron, Helsinki, Finland, A. S. Dontas, Athens, Greece, M. J. Karvonen, Helsinki, Finland, and Ancel Keys, Minneapolis, Minnesota

The carotid pulse wave in supine rest was recorded on two occasions, five years apart, in strictly random samples of rural men, initially 40 to 49 years old in defined areas of East Finland ($N = 177$) and West Finland ($N = 137$). An externally applied capsule was connected to a Statham P23AA pressure transducer and the am-

plified output together with an ECG lead for timing, was recorded on an Elema Mingograph. Re-test on 80 men gave reliability coefficients of 0.69 to 0.94 for the pulse parameters.

In general, five-year changes in pulse wave tended to correspond to average age trends we observed in cross-sectional studies. Among the men initially 40 to 44 years old, the five-year changes were similar in the two regions, but among the men initially 45 to 49 the changes were greater ($P < 0.05$) in "peak time" (wave foot to maximum amplitude) and "relative peak time" (peak time/cycle time) in East than in West Finland. The carotid pulse findings appeared to be unrelated to blood pressure. The greater aging change in East as compared with West Finland may have significance in regard to the fact that the incidence of coronary heart disease is markedly higher in East than in West Finland.

Thrombogenic Effects of Albumin-bound Fatty Acids (P)

John C. Hoak, William E. Connor, and Emory D. Warner, Iowa City, Iowa

Unbound long-chain saturated fatty acids produce generalized thrombosis and sudden death when injected intravenously into animals. Since fatty acids usually are transported in the blood bound to albumin, the present study was performed to evaluate the possible thrombogenic effects of albumin solutions containing a high concentration of stearic acid.

Fifteen normal rabbits received intravenous injections of 5% bovine albumin solution containing added stearate, (10 ml/kg body wt over a 5 min period). The albumin-stearate combination was a clear solution with a final free fatty acid (FFA) concentration of 1,400 to 2,100 μEq/L. A jugular vein segment was occluded immediately following injection of the albumin solution, and examined for thrombi 15 minutes later. The animals were then heparinized, killed with pentobarbital and autopsied. Similar studies were performed in ten control rabbits which received infusions of the same albumin without added stearate (FFA concentration, 200 to 400 μEq/L).

Eight of 15 rabbits which received injections of the albumin with a high stearate concentration developed lung thrombi, and ten formed jugular thrombi. In contrast, none of the control group had lung thrombi and only five formed thrombi in the jugular segment.

Whole-blood silicone clotting times were performed before and immediately after the albumin infusions. Significant shortening ($P < 0.01$) was observed with the albumin-stearate group (before, 37.8 min $\pm$ SE 3; after, 23.2 $\pm$ 3), but not with the albumin controls (before, 35.5 $\pm$ 2.5; after, 30.8 $\pm$ 3.7).

Albumin solutions containing a high concentration of stearic acid did not cause sudden death but did produce hypercoagulability and thrombosis on most instances.

Comparative Effects of d-Thyroxin and Ethyl p-Chlorphenoxyisobutyrate on Body Cholesterol Metabolism in Man (P)

William Hollander and Aram V. Chobanian, Boston, Massachusetts

The effects of d-thyroxin and ethyl p-chlorphenoxyisobutyrate (CPIB) on body cholesterol metabolism have been studied in 20 hypercholesterolemic subjects. The effects of the drugs on the conversion of intravenously administered C^{14}-acetate and C^{14}-mevalonic acid into plasma cholesterol and on the miscible pool and turnover rate of cholesterol have been determined. D-thyroxin (4 mg/day) reduced serum cholesterol by 24% but did not alter the miscible pool of cholesterol. However, it did increase the turnover rate of cholesterol by 42%. The conversion of acetate and mevalonic acid into cholesterol was not altered by d-thyroxin. CPIB (2 g/day) reduced the serum cholesterol by 21% and the miscible pool of cholesterol by 38%. The cholesterol-lowering effects of CPIB were associated with a 41% decrease in the conversion of C^{14}-acetate into cholesterol. In one subject with hypercholesterolemia and xanthomatosis, in whom cholesterol formation from acetate was abnormally high, CPIB decreased the conversion of acetate to cholesterol by 83%. These effects of CPIB were accompanied by a 37% reduction in serum cholesterol and a marked regression of the xanthomata. Desmosterol was not detected in significant amounts in the plasma during CPIB and d-thyroxin therapy. In conclusion, d-thyroxin increases the turnover rate of cholesterol and reduces serum cholesterol without significantly changing the miscible pool of cholesterol. CPIB decreases both serum cholesterol and the cholesterol miscible pool as an apparent result of inhibition of cholesterol biosynthesis.

Effect of Diethylstilbestrol on Cholesterol in Male Rats (P)

Louis Horlick, Saskatoon, Saskatchewan, Canada

Male Wistar rats weighing approximately 250 g were divided into five groups of six animals each (A-E). Groups B-E received diethylstilbestrol in peanut oil intramuscularly for five days of each week in doses of 600, 300, 75 and 18.75 mg/kg body weight. The control group (A) re-

ceived peanut oil only. Injections were given for three weeks.

All stilbestrol-treated animals failed to gain weight and showed testicular atrophy and adrenal hypertrophy. Serum cholesterol levels were reduced in the treated animals and serum lipid phosphorous increased slightly. (Cholesterol: A, 71 ± 7.5 mg %; B, 62 ± 15.5; C, 60 ± 18.4; D, 52 ± 7.8; E, 63 ± 16.8. Lipid P: A, 6.6 ± .6 mg %; B, 7.3 ± 1.3; C, 9.2 ± 2.1; D, 7.8 ± 1.1 E, 10.7 ± 1.8.) Liver cholesterol was slightly increased in the treated groups.

Liver slices from the treated animals incorporated more C^{14}-acetate into liver cholesterol than did the controls. (A, 49,251 ± 23,955 cpm/g liver; B, 83,931 ± 52,277; C, 99,468 ± 33,400; D, 93,821 ± 32,651; E, 76,119 ± 29,227.)

Fecal sterols and bile acids were measured on samples collected prior to injection and again during the final week of the experiment. Total fecal bile acids were increased in the treated groups (A, 0.067 ± 0.017 mEq/10 g dry weight; C, 0.106 ± 0.020; D, 0.103 ± 0.011; E, 0.095 ± 0.018), but there was no change in fecal sterol excretion. There was a striking change in the pattern of individual fecal bile acid excretion during stilbestrol treatment.

Our results suggest increased conversion of cholesterol to bile acids and increased losses of the bile acids in the stool during stilbestrol treatment and offer a possible explanation for the paradox of decreased serum cholesterol in the presence of increased hepatic biosynthesis.

Fate of Platelet Mural Thrombi in Swine Arteries (P)

Leif Jorgensen, Toronto, Ontario, Canada, Harry C. Rowsell, Guelph, Ontario, Canada, Torstein Hovig, and James F. Mustard, Toronto, Ontario, Canada

Mural thrombi have been implicated as a factor in the formation of atherosclerotic plaques. Arterial thrombi are platelet-rich. Platelet emboli in rabbit pulmonary arteries transform into intimal thickenings rich in foam cells, while fibrin emboli give rise to fibrous plaques. In the present study, the fate of platelet-rich mural thrombi in normal swine arteries was investigated by light and electron microscopy. Thrombi were produced by placing silk sutures or collagen fibers in carotid arteries. One-hour-old thrombi were composed of platelet masses with leukocytes, a few red cells, and strands of fibrin around the periphery. There was no evidence of fibrin binding the platelets together. Platelets in the periphery were swollen and had lost their organelles but had intact boundary membranes. Platelets in the thrombus center showed small ultrastructural changes. By 24 hours the platelets were almost all lysed, with fibrin present throughout the shrunken thrombus. Endothelium near the thrombus, intact at one hour, had frequently disappeared by 24 hours. Mononuclear cells, many of which had phagocytosed platelets and debris, were evident. By four to seven days, the mass was covered with endothelium. Mononuclear cells were increased and frequently elongated. By 14 to 21 days, the lesion was rich in smooth muscle cells and collagen, with traces of fibrin and cellular debris. The end result was a lipid-poor intimal lesion, rich in smooth muscle cells similar to spontaneous fibrous plaques in the pig.

Changes in Blood Catecholamines with Smoking

Udomporn Kashemsant, Harold Smulyan, and Robert H. Eich, Syracuse, New York

Although the hemodynamic and metabolic effects of cigarette smoking have been attributed in part to the release of catecholamines, their circulating blood levels have not been measured. This study was carried out in 18 subjects (ten nonsmokers and eight smokers) to measure changes in norepinephrine (NE) and epinephrine (E) during and following the smoking of a single cigarette. In addition, the changes in blood pressure (BP), pulse, and the arterial and venous level of lactate, pyruvate, glucose and free fatty acids (FFA) were measured. With smoking, BP increased in all except two subjects (mean increase, 10 mm Hg systolic and 4 mm Hg diastolic). The pulse rose six beats per minute, Arterial NE increased in all except three (mean increase, 0.23 ± 0.17 μg/L, and E rose in only two. Arterial FFA increased 300 ± 60 μEq/L. There was no change in glucose, lactate, or pyruvate. Although NE did increase, there was no correlation between the increase in NE and the changes in BP, pulse, or FFA.

Effect of Cigarette, Cigar, and Pipe Smoke Inhalation on Serum Lipid Concentrations and Urinary Catecholamine Excretion in Dogs

Alfred Kershbaum, Samuel Bellet, Young W. Cho, and Jutta E. Dugge, Philadelphia, Pennsylvania

Studies in human subjects have shown that cigar smoking results in significantly less mobilization of free fatty acids (FFA) and excretion of catecholamines than cigarette smoking. Observations on the influence of inhaling on the FFA response indicated that the degree of FFA elevation was affected by the presence or absence of inhaling during either cigar or cigarette smoking. It was suggested that the smaller FFA rise with

cigar smoking was due to the absence of inhaling (less nicotine absorption).

To further explore this, experiments were performed in chloralosed dogs in which the degree of inhalation was kept constant. Using airtight tracheal intubation, respiration was maintained at a constant rate and volume by a positive-pressure animal respirator. The smoke from a measured quantity of tobacco was delivered to the trachea in a fixed time interval by means of a manifold smoke-mixing valve attached to the intake port of the respirator. Each dog inhaled cigarette, cigar, and pipe smoke on different days in random sequence. Two cigarettes (2 g tobacco), 2 g of cigar, or 2 g of pipe tobacco (each having approximately 2% nicotine content) were smoked in a ten-minute period. Serum FFA, triglycerides, and cholesterol concentrations were determined in venous blood samples taken before and after intubation, after smoking, and 10, 30 and 50 minutes later. In 12 dogs, mean FFA rise with cigarette, cigar, and pipe smoke was $38 \pm 8\%$, $34 \pm 7\%$ and $35 \pm 14\%$, respectively. Mean triglyceride increment was $26 \pm 4\%$, $29 \pm 6\%$ and $27 \pm 4\%$. The differences in response were not statistically significant. There was no effect on serum cholesterol. Lipid effects of intravenous nicotine were similar to those of tobacco smoke. Blood radioactivity curves were similar after inhalation of smoke from cigarettes and cigars containing C^{14}-glucose (random-labeled).

Total free catecholamines were measured in urine collected from catheterized dogs during a four-hour smoking period. There was no significant difference in catecholamine excretion with cigarette, cigar, or pipe smoking, or intravenous nicotine.

These results demonstrate that if the degree of inhalation is constant, there is no difference in the effect of cigarette, cigar or pipe smoking on blood lipids or urinary catecholamines.

Quantitative Determination of Lipoproteins by Electrophoresis

George C. Klein, Janet E. Fetner, Rawser P. Crank, Jr., and Gerald R. Cooper, Atlanta, Georgia

A modified paper electrophoretic method for determination of lipoprotein utilizes a tris-EDTA-borate buffer system to sharpen alpha-lipoprotein fraction and employs pre-staining with an ethyl acetate-propylene glycol solution of Sudan Black B to minimize background discoloration. This technique provided better quantitation of ratio of beta- to alpha-lipoproteins than procedures using barbital buffer for separation of components and oil red 0 or fat red 7B dye for staining. Residual dye at the point of application seems to limit estimation of chylomicrons. Except for this residual dye, patterns yield components similar to those of Lees and Frederickson. Quantitation is necessary to detect alterations in lipoproteins in normal individuals or those with mildly abnormal lipid changes.

Preliminary clinical evaluation of the method included analysis of serum from apparently normal individuals, patients with suspected lipid disorders, and persons undergoing fat tolerance studies. The types of lipoprotein patterns are consistent with the classification of Frederickson and Lees. Lipoprotein changes in five nondiabetic postabsorptive subjects after ingestion of standard amounts of corn oil and coconut oil showed quantitative changes in components but no change in pattern type. No difference in effect of the two ingested fats on serum lipoproteins was noted. The pre-beta component was induced in one diabetic subject and accentuated in one nondiabetic, hyperglyceridemic person after fat ingestion. Generally, decreases in the percentage of the electrophoretic alpha-lipoprotein component tended to parallel elevations in serum triglyceride of the patients undergoing fat tolerance tests.

Influx and Distribution of Intravenously Administered Radioactive Cholesterol in Experimental Atherosclerosis of Dogs

Dieter M. Kramsch, Gosuke Inoue, Ira Gore, and William Hollander, Boston, Massachusetts

The influx of cholesterol into arteries was measured following injection of C^{14}-cholesterol into dogs with experimental atherosclerosis induced by feeding thiouracil and high-cholesterol diet. The distribution of H^3-cholesterol in arteries was determined by a new radioautographic method four weeks after the intravenous injection of the labeled cholesterol. The influx of C^{14}-cholesterol into arteries of atherosclerotic dogs was two to seven times higher than into arteries of normal control dogs. In atherosclerotic dogs, the cholesterol influx was two to five times greater into aortic plaques than into adjacent normal appearing aorta. However, cholesterol specific activities in plaques and adjacent "normal" aorta were comparable. Radioautography revealed not only a diffuse concentration of H^3-cholesterol in the aortic plaques but also in the adjacent histologically normal aorta in subintimal areas of the media. This accumulation of H^3-cholesterol was not related to any particular structure of the aortic wall, whereas in normal control dogs radioactive cholesterol was concentrated along the elastic membranes of the media. The histologically unaltered coronary arteries of atherosclerotic dogs also showed accumulation of H^3-cholesterol

between elastic membranes instead of concentrations along the elastic membranes of the media. Peripheral muscular arteries revealed diffuse accumulation of H^3-cholesterol while peripheral arteries of normal control dogs did not. In conclusion: (1) The influx of cholesterol is increased in arteries of atherosclerotic dogs. (2) Radioactive cholesterol is diffusely distributed within plaques and the media of histologically normal arteries, whereas in normal control dogs it is concentrated along elastic membranes of the media.

Effect of Carbohydrate Metabolism Upon the Fatty Acid Composition of Plasma Lipids of Patients with Familial Hypercholesteremia

Peter T. Kuo, Philadelphia, Pennsylvania

A number of investigators have found that plasma lipids of hypercholesteremic and atherosclerotic patients have less polyunsaturated and more saturated fatty acids than normal subjects. These observations led to the belief that hypercholesteremia and atherosclerosis may result from essential fatty acid deficiency. This study suggests that an altered carbohydrate metabolism may well account for the observed changes in the fatty acid pattern of the plasma lipids in hypercholesteremic patients.

Fatty acid composition of plasma triglyceride, cholesterol ester, and lecithin was determined in seven patients from three families with essential familial hypercholesteremia while they were on: (1) home diet, (2) and (3) high- and low-carbohydrate (sugar) diets, and (4) tolbutamide treatment. The amount of unsaturated fat intake in the home diet was maintained. Body weight was kept constant. Eight normolipemic family members served as control study for the plasma lipid pattern of normolipemic subjects on a home diet. The results were: (1) Increases in the C_{16} and C_{18} saturated and monounsaturated fatty acids with decreases in the polyunsaturated fatty acids as compared with controls were observed in the plasma lipids of these patients. (2) This pattern was exaggerated by high carbohydrate feeding. (3) The abnormality was partially corrected by carbohydrate restriction. (4) The pattern became normal following carbohydrate restriction and tolbutamide administration. Hypercholesteremia was rigorously maintained by these patients during the feeding periods; but it was gradually lowered by low carbohydrate intake plus tolbutamide administration.

The study suggests that hypercholesteremic patients may divert a major portion of their carbohydrate metabolism towards lipid synthesis to maintain hypercholesteremia and to induce a relative decrease in the polyunsaturated fatty acid content of their plasma lipids.

Biochemical and Morphological Events Preceding and Accompanying Atherosclerosis in Rats: Protein Synthesis by Subcellular Fractions From Aorta and Liver

Kyu Taik Lee, Dong Nack Kim, Rose Jones, and Wilbur A. Thomas, Albany, New York

Thrombosis and arterial changes characterized by intimal smooth muscle cell proliferation and collagen can be produced in rats by complex diets in a period as short as one month. Experiments reported here involving biochemical and electron microscopy studies of subcellular fractions from 450 rats are the second of a series designed to determine the nature and sequence of biochemical and morphological events that precede or accompany these pathological changes during a dietary period of 0 to 30 days. One group was fed, among other ingredients, cholesterol, peanut oil, sodium cholate and thiouracil, and another group received stock diet. Fibrinogen levels rose from 200 mg % at 0 hour to 252 mg % at 18 hours on diet, 310 mg % at 48 hours, and 450 mg % by 30 days. Rate of incorporation of C^{14}-leucine into hepatic microsomal protein in a cell-free system per unit of RNA changed only slightly in first two weeks, and by 30 days had decreased rather than increased. Similarly, studies of subcellular protein-synthesizing systems from aortae indicate decreased incorporation of C^{14}-leucine per unit of RNA by 30 days, in spite of the fact that by this time intimal proliferation of smooth muscle cells and excessive collagen formation begins to become evident in some of the rats. DNA content per unit weight of aortic tissue increased 2.4 times and RNA 1.5 times by 30 days. These somewhat paradoxical observations suggest several lines for future investigation, including study of factors related to fibrinogen degradation and relation of inhibitors of DNA synthesis in arterial walls to protein synthesis.

Localization and Pattern of Lipids in the Bovine Aortic Wall With or Without Spontaneous Gross Lesions

Ivan N. Likar, Lydia J. Likar, Roger W. Robinson, and Robert S. Bennett, Worcester, Massachuetts

The abdominal aortae of 100 cows, five to ten years of age, were examined grossly. Representative sections were selected from areas near the coeliac(I), renal(II), utero-ovarian arteries(III), and the bifurcation of the aorta(IV), for histochemical and biochemical examination. Some aortae were grossly yellow, particularly in regions III and IV and around the ostia of branches. These yellow streaks and often the periphery of elevated lesions were stained with oil red 0.

Histochemical examination revealed lipids in 24% of grossly normal aortae. They were present in the intima and inner part of the media of 4% from area I, 8% from II, 13% from III, and 20% from IV. In aortae with gross lesions lipids were seen in 44, 40, 64 and 64% at corresponding sites. Phospholipids, especially sphingomyelin, increased with slight lesions and decreased with advanced disease. Free fatty acids increased in proportion to the severity of lesions.

Thin-layer chromatograms of lipids extracted from bovine serum and each of the four areas of the aorta were obtained. Aortic tissue contained more phospholipids than serum. Severe lesions showed a decrease in phospholipids and triglycerides, with an increase in free fatty acids and cholesterol esters. In aortae without lesions, the dry matter represented 280 to 330, total cholesterol 0.79 to 0.92, and total lipids 13.0 to 31.6 mg/g of the wet weight. The corresponding values in aortae with gross lesions were 270 to 410, 0.7 to 1.7. and 6.8 to 55.4 mg/g, respectively.

Acid Mucopolysaccharides in the Urine of Women

Lydia J. Likar, Ivan N. Likar, Roger W. Robinson, and Servada Mishra, Worcester, Massachusetts

Acid mucopolysaccharides (AMPS) and the AMPS-creatinine ratio (A/C) were determined at different stages of ten menstrual cycles in the urine of two young women (AMPS values expressed as mg of hexuronic acid). Woman I had 1.9 to 4.4, woman II 1.8 to 5.8 mg AMPS/24 hr. Variations were observed during the cycle with a significant decrease of AMPS in the progestational phase, average 38%, from 3.88 to 2.47 mg, reaching the lowest values the seventeenth, eighteenth or nineteenth day of the cycle.

Values of AMPS and A/C ratio in the urines of three postmenopausal women remained constant in nearly a straight line pattern through 15 collections (every second day for one month) for each woman. Woman A had 3.7 to 4.2, woman B 4.4 to 5.4, woman C 2.8 to 3.3 mg AMPS.

AMPS and A/C in the urine of postmenopausal women treated with conjugated equine estrogens showed a quick response to the treatment. Woman A had 2.8 to 5.6 mg, average 4.2 mg AMPS. The limited number of observations to date does not allow further discussion.

The percentage change of AMPS values in the urine of women during the ten menstrual cycles varied from 35 to 63, in postmenopausal urine from 12 to 19, and during estrogen treatment by 50%.

This investigation disclosed that hormones which regulate the menstrual cycle influence the excretion of AMPS in the urine.

A noticeable amount of a 0.75 M NaCl fraction was separated by Dowex column chromatography.

Metabolic Patterns of Atheromatous Pigeon Aortae (P)

Hugh B. Lofland, Jr., Thomas B. Clarkson, and John E. MacNintch, Winston-Salem, North Carolina

A technique has been devised which allows pigeon aortae to be perfused with blood serum containing isotopically labeled substrates (C^{14}-acetate for studies of lipid synthesis, S^{35} for mucopolysaccharide synthesis, or C^{14}-glucose for carbohydrate metabolism). These aspects have been studied in pigeon aortae in which atherosclerosis varied from very slight to very severe.

Enhanced synthesis of fatty acids from acetate is seen in moderate or severely diseased aortae, but not in the fatty streak stage. There was no increase in deoxyribonucleic content of aortae as atherosclerosis progressed.

In regard to carbohydrate metabolism, pigeon aortae metabolize more glucose via the hexose monophosphate pathway than via glycolysis during perfusion. However, neither total glucose consumption nor the ratio of the two different pathways appeared to be influenced by the severity of atherosclerosis.

The synthesis of acid mucopolysaccharides from sodium sulfate-S^{35} was compared among very young nondiseased pigeons, young pigeons fed cholesterol for one month, and 7- to 8-year-old pigeons having naturally occurring atherosclerosis. No significant differences in mucopolysaccharide synthesis were detected between the first two groups. Both groups, however, synthesized more than did the older birds in the latter group.

Strong positive correlations were found between the levels of serum cholesterol and the amounts of lipid synthesized from acetate during perfusion, and similarly between aorta cholesterol and lipid synthesis.

Effects of Pregnancy and of Hormone Treatment on Arterial Structure and Atherogenesis in Rabbits

Pacita Manalo-Estrella, C. Bruce Taylor, and A. Kaye Asdel, Evanston, Illinois

Specific alterations in the elastica, collagen, muscle, and ground substance of the aortic media of pregnant rabbits and rabbits treated with a synthetic progesterone-like hormone have been demonstrated by histochemical methods. These effects on the rabbit vasculature were found to be tran-

sient. Regression rates after the withdrawal of the stimulus were variable. In the postpartum rabbit aortae, the changes in the connective tissue were virtually normal within 15 days after delivery. In the hormone-treated rabbits, the regression of the connective tissue to normal was observed by the tenth day after cessation of treatment. Both in the postpartum series and in the hormone-treated rabbits, it appeared morphologically that the acid mucopolysaccharides had returned to normal immediately after the withdrawal of the stimulus. The changes in the ground substance seen histochemically were quantitated by labeling the acid mucopolysaccharide with radioactive sulfate and autoradiography. An increase of aortic acid mucopolysaccharide between the first and fifteenth postpartum day was demonstrated by autoradiography. By histochemical methods, this was not detected. The increase probably corresponds to the time when reparative processes and edema are most prominent.

The specific vascular changes as the result of pregnancy and progesterone-like hormone treatment in rabbits were compared to the changes observed in atherosclerotic aortae of high-cholesterol-fed rabbits and to another group of high-cholesterol-fed rabbits which were subjected to the same progesterone-like hormone treatment.

Verification of morphologic findings is being correlated with aortic distensibility by mechanical methods.

Role of Alternate Pathways in Cholesterol Synthesis (P)

Mary L. Mobberley and Ivan D. Frantz, Jr., Minneapolis, Minnesota

Work from several laboratories has established the ability of lathosterol (Δ^7-cholestenol) and desmosterol ($\Delta^{5,24}$-cholestadienol) to serve as intermediates in cholesterol synthesis. No reasonable biogenetic scheme can be visualized in which both of these compounds could participate in a single pathway.

When liver slices from normal rats were incubated with an excess of sodium acetate-1-^{14}C, radioactivity entered cholesterol almost linearly between 30 minutes and three hours. Radioactivity in the sterol intermediates also increased linearly for about two hours and then plateaued. The maximal rate of increase in cholesterol was over 30 times that in either lathosterol or desmosterol. When labeled acetate was infused continuously into the portal vein, radioactivity increased linearly in the precursors for 90 minutes at a rate comparable to the rise of radioactivity in cholesterol. In intact rats whose body water was maintained at a constant level of labeling with tritium, the plateau of isotope in the precursors was not reached before at least 48 hours. These relationships are most easily explained on the assumption that at least two pools of each intermediate are present.

In rat liver homogenates, the time required for maximal isotope content in the precursors was less than 20 minutes, but evidence for slowly metabolizing pools was still present. It could be concluded that, under these conditions, at least one-fifth of the radioactivity reaching cholesterol passed through desmosterol, but that the pathway through lathosterol was probably quantitatively more important.

Inhibition of Atherosclerosis in Monkeys by Chondroitin Sulfate A (P)

Lester M. Morrison, Katsumi Murata, J. Joseph Quilligan, Ole A. Schjeide, and Leon Freeman, Los Angeles, California

Effects of acid mucopolysaccharides (AMPS), including chondroitin sulfate A (CSA), heparin, and calf aorta extract (EXT), on experimental atherosclerosis induced by cholesterol-butter feeding were studied in the squirrel monkey (*Saimiri sciurea*). Sixty-five young males and females initially averaging 0.55 kg were divided into six groups: (1) ten controls, normal diet, (2) 15 cholesterol-butter fed (CBF), (3) ten CBF plus daily saline injection, (4) three groups of ten CBF plus daily subcutaneous injections of 10 mg chondroitin sulfate A, heparin, or EXT. The CBF diet contained 1.5 g of cholesterol and 20 g of butter per day. Serum cholesterol determinations, performed monthly, showed wide individual variations. The animals were sacrificed after nine months of study.

Remarkable inhibition of atherosclerosis was observed in the CSA-treated group as compared to the CBF group. Further, the aortae of CSA-treated monkeys showed fewer lesions than those of any of the other five groups, including that on a non-cholesterol-butter diet. Monkeys receiving heparin and CBF controls had moderately severe atherosclerotic involvement of the aortae. Six of the EXT group died prior to sacrifice, possibly from anaphylactoid reactions. Four survivors displayed extensive atheromatous lesions.

Isotopic studies of the action of CSA in tissue cultures suggest that its anti-atherosclerosis effect may be mediated by acceleration of lipid and protein metabolism in the aortic cells with a consequent lowering of total cellular lipid.

Smooth Muscle Alterations in Injured Muscle Arteries (P)

Marvin Murray, G. Randolph Schrodt, and Harold F. Berg, Louisville, Kentucky

It has been demonstrated by us and others that smooth muscle cells undergo structural

changes in spontaneous and enzyme-induced atherosclerosis. To our knowledge there have been no ultrastructural studies of anastomosed muscle arteries, although the structure of graft anastomoses has been studied in detail. In the present study, the femoral and brachial arteries of dogs were incised to one-half their circumference, and reanastomosed with Teftek thread. The anastomosed areas were removed from one day postanastomosis to four weeks postanastomosis. Sections were studied by light and electron microscopy.

The following observations were noted: Fibroblasts of the adventitia proliferated and laid down collagen healing the adventitia. In the media, smooth muscle cells directly traumatized by knife, needle, or suture became necrotic, as did the endothelial cells. Smooth muscle cells immediately adjacent exhibited changes in their fine structure. These changes consisted of a dissolution or pushing of the myofilaments to the periphery of the cell, and expansion of the endoplasmic reticulum and a proliferation of ribosomes. Occasional lipid bodies were seen within these cells. Immediately adjacent to these altered cells, masses of collagen fibrils were seen, suggesting that these cells participate in collagen production. These altered smooth muscle cells have characteristics of fibroblasts as well as smooth muscle cells, indicating that the vascular smooth muscle cell is an uniquely primitive cell, capable of metabolic and structural transformations. The data suggest that in the muscle artery, smooth muscle cells heal the media without the participation of fibroblasts from the adventitia.

Mechanisms of Uptake and Release of Cholesterol from Rabbit Atherosclerotic Aortae (P)

Howard A. I. Newman and D. B. Zilversmit, Memphis, Tennessee*

Studies were undertaken to answer the question: Is C^{14}-cholesterol in atheromatous lesions of C^{14}-cholesterol-fed rabbits derived from plasma by an exchange mechanism, a filtration, or an energy-requiring process? Since lipoprotein-bound free cholesterol is known to exchange but cholesterol ester presumably does not, the accumulation of C^{14}-cholesterol ester in the aorta would have to be either a direct influx of plasma cholesterol ester or an influx of free cholesterol, possibly by exchange, with subsequent esterification in the aorta. To decide between these mechanisms, plasma from hypercholesterolemic atheromatous rabbits labeled with free C^{14}-cholesterol only, was reinjected autologously. The plasma C^{14}-cholesterol ester specific activity increased linearly in either six or ten hours, but only represented a small percentage of the plasma free cholesterol specific activity. Less than 5% of the C^{14}-cholesterol ester in atheroma can be accounted for by esterification of aortic free C^{14}-cholesterol. Therefore, 95% of the C^{14}-cholesterol ester found in the aorta must come directly from plasma.

In addition, aortae were incubated with plasma from C^{14}-cholesterol-fed hypercholesterolemic rabbits. The uptake of C^{14}-cholesterol in vitro was the same as that of the aorta in the intact animal, which is evidence against the filtration theory. The boiling of atheromatous aortae did not stop entry of C^{14}-cholesterol. Adding 5×10^{-2} M CN^- and F^- enhanced uptake of C^{14}-cholesterol and cholesterol ester. Apparently, entry of cholesterol into atheromas is not an energy-requiring reaction, but energy may be required to limit the entry of cholesterol into arteries.

Use of Heparin and Oral Anticoagulants for Impending Myocardial Infarction

E. Sterling Nichol, William C. Phillips, and Richard A. Elias, Miami, Florida

Since 1937, numerous reports suggest that many patients developing myocardial infarction experience prodromata with acceleration of anginal pattern for days or weeks. The diagnosis of impending infarction rests squarely on the patient's story, but it is necessary to make sure a slight infarction has not already taken place. Pathological correlations have been described.

Since 1947, the senior author has treated all such private patients with rest, sedation, coronary vasodilators, and prompt heparinization followed by oral anticoagulants. The results in 318 patients have been published. The present study depicts the outcome of the regimen in 97 new patients. Of these, 42 had suffered one or more previous infarctions. There were 73 men and 24 women, aged 31 to 80 years. Hypertension was found in 43 (44.3%) congestive heart failure in 40 (41.2%) and diabetes in ten (10.3%).

Results: Eight patients (8.3%) developed either transmural or subendocardial infarction within 60 days, without mortality in the following two months. In the remaining 89 patients, no laboratory, clinical, or cardiographic signs of myocardial necrosis appeared, although recurring transitory electrocardiographic ischemic patterns were sometimes observed. A properly constructed clinical trial of anticoagulant therapy has not been made by us or others because the ethical implications are too grave to permit withholding anticoagulant therapy in patients with threatened myocardial infarction. Close clinical observation convinces us that the most rewarding use of anticoagulant therapy in patients afflicted with cor-

onary atherosclerotic heart disease is during impending infarction.

Serum Lipid Changes Produced by Lipoprotein Lipase in Normal and Hyperlipidemic Subjects

Robert P. Noble, Sharon, Connecticut

The effect of heparin-induced, 0.1 mg/kg, lipoprotein lipase activity (LPL) on fasting serum triglyceride (TG) and cholesterol levels was studied in 22 normal and in 15 hyperlipidemic subjects. In the normals, the mean serum TG reduction of 44.4 mg per 100 ml occurred within 20 minutes after injection and remained unchanged for one hour, at which time LPL activity was virtually zero and free fatty acids (FFA) had declined from a mean post-heparin peak value of 1,200 μEq/L to the pre-heparin value. In the hyperlipidemic subjects, a similar pattern was found, except that the mean TG reduction was 112.0 mg % while the mean FFA peak reached 1,602 μEq/L. The decrease in serum TG was insufficient to bring about lipemia clearing. Tests for LPL inhibition were negative. Subsequently, three injections of heparin 30 minutes apart were employed. The rise of LPL and FFA after each injection was prompt. Chylomicrons and very low-density ($D < 1.007$) lipoproteins were separated from each pre- and post-heparin sample by two successive centrifugations. Normal serum did not contain chylomicrons. In these subjects, the VLDL contained a mean of 65.3 mg % TG and 36 mg % cholesterol. These values were reduced by 91% and 79% respectively after heparin injection. In four fasting hyperlipidemic subjects restudied thus far, chylomicronemia, 83.6 mg %, persisted throughout three heparin injections. In the VLDL fraction, which in these cases contains the non-alimentary light-scattering "hepatomicrons," the reduction of TG and cholesterol was less than 50% of the totals, 417.7 mg % and 108.3 mg %, measured therein.

Studies of the Rat Liver Lipolytic Activity (P)

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The mammalian liver contains several enzymes which might be concerned with the hydrolysis of liver lipids. Unfortunately, the liver aliesterases have not been clearly differentiated from lipase. In this study, classification of enzymes catalyzing hydrolysis of various esters is based on the physical-chemical state of substrates. According to Desnuelle, lipases act on emulsified long-chain triglycerides, and esterases on soluble esters of low molecular weight.

An enzyme preparation catalyzing the hydrolysis of long-chain triglyceride was isolated from rat liver homogenates and partially purified by butanol fractionation and Sephadex gel-filtration. The substrate consisted of Ediol emulsion and sodium deoxycholate, and the activity was determined by titrating the liberated fatty acids. The pH optimum of the preparation was between 7 and 7.2. There was a linear relationship between the rate of lipolysis and both the time of incubation and the substrate concentration.

No inhibition of activity was demonstrated using known ali-esterase inhibitors. However, the addition of an emulsified preparation of diethyl-p-nitrophenyl phosphate caused an 80% inhibition of lipolytic activity. Further differentiation between esterase and lipase activities was made by using an aqueous solution (0.5%) and emulsions of methyl butyrate as substrates.

Studies on the subcellular distribution of lipase and esterase activities showed the localization of maximal lipase specific activity in the soluble fraction and the maximal esterase specific activity in the microsomal fraction.

Some Factors Controlling Localized Permeability in the Aorta

Marian A. Packham, Harry C. Rowsell, Michael F. Glynn, and James F. Mustard, Toronto, Ontario, Canada

The pattern and extent of increased permeability of the aorta was studied in pigs using Evans Blue and I^{131} albumin. The areas of blueing were focal and the I^{131} followed the blueing pattern. In young normal pigs, the aortic arch and valve regions showed the most intense blueing and these contained more I^{131} than adjacent pale areas. Blueing also occurred around vessel orifices and the aortic trifurcation, which are characteristic sites of early swine atherosclerosis, interaction of the formed elements with the vessel wall, and transient mural thrombi. Diffuse endothelial injury in regions of focal increased permeability produced generalized blueing and greatly increased I^{131} accumulation. This suggests that the focal regions of increased permeability may be caused by localized injury. The interaction of formed elements with the vessel wall or transient mural thrombi in regions of disturbed flow may be a factor. Components of white cells can increase vessel permeability, and we found that aggregated platelets also release factors which increase vessel permeability. When platelet-leukocyte thrombi are induced on the aortic surface, there is a marked local increase in permeability. Because serotonin is one platelet component influencing vessel permeability, eight pigs were given reserpine to deplete their platelets of serotonin. The blood pressure remained within

normal limits. Aortic permeability was diminished by more than 60% in these animals. Interaction between the formed elements and the vessel wall may be a factor in causing the focal areas of increased permeability.

Serum Uric Acid Levels in Hypercholesteremic Individuals, With and Without Hypertriglyceridemia

William B. Parsons, Jr., Madison, Wisconsin

The relationship between serum levels of uric acid and serum lipids, particularly cholesterol, has been studied by numerous authors and recently reviewed by Berkowitz, who reported his observations in hypercholesteremic individuals with and without hypertriglyceridemia. His patients, garment workers mainly of Jewish or Italian extraction, showed a striking difference in incidence of hyperuricemia—82% in subjects (41/50) with hypertriglyceridemia but none (0/50) in subjects with normal triglycerides. These findings prompted a similar review in hypercholesteremic patients currently being followed by our laboratory.

Cholesterol, triglycerides, and uric acid were determined on fasting serum from 100 hypercholesteremic individuals, 63 of whom had elevated triglycerides (exceeding 150 mg %). The hypertriglyceridemic group included 26 women, 37 men; those with normal triglycerides included 17 women, 20 men. All were of European lineage, with preponderance of German and Scandinavian ancestry.

Hyperuricemia (exceeding 6.0 mg %) was found in 16.2% (6/37) of patients with normal triglycerides and 41.3% (26/63) of hypertriglyceridemic patients. Mean uric acid levels were 4.9 mg % in the normal triglyceride group, 5.6 mg % in hypertriglyceridemic individuals. While confirming the more precise association of hyperuricemia to hypertriglyceridemia than to hypercholesteremia, this study failed to demonstrate the absence of hyperuricemia in hypercholesteremic patients as suggested by Berkowitz. The differences in incidence of hyperuricemia in his series and this one are probably related to the aforementioned differences in national origins.

Long-Term Therapy with Nicotinic Acid and Aluminum Nicotinate in Hypercholesteremic Individuals: Results in Ninety-Nine Patients Treated for One to Nine Years

William B. Parsons Jr., Madison, Wisconsin

Since 1956, 99 hypercholesteremic patients have been treated at the Jackson Clinic with nicotinic acid preparations for periods exceeding one year. Twenty-five patients have completed five to nine years of therapy, nine patients four to five years, 15 patients three to four years, 19 patients two to three years, and 31 patients one to two years. Plain nicotinic acid (NAc) and aluminum nicotinate (AlN) have been used extensively; other niacin modifications proved less satisfactory. Dosage must be individualized, usually starting at 1.0 g t.i.d. with NAc, 0.5 g t.i.d. for AlN, and increasing if necessary to achieve adequate hypocholesteremic response.

In 88 patients, comparison of mean serum cholesterol levels during all control periods (310 mg %) with mean values during NAc therapy (244 mg %) showed reduction of 21.3%. Similar comparison in 61 patients on AlN (control 297 mg %, treatment 244 mg %) showed reduction of 14.5%. Use of both drugs consecutively in 50 patients (control 298 mg %, NAc 239 mg %, AlN 245 mg %) showed no significant difference between their hypocholesteremic efficacy. Mean values during therapy would be lower if results during suboptimal dosage were eliminated, particularly since several dosage levels of AlN were systematically studied at one time. Reduction in beta-lipoprotein cholesterol and serum triglycerides accompanies cholesterol reduction.

Flushing from plain NAc usually disappears early but, if persistent, is minimized by substituting AlN. Nausea, rare on NAc but more common on AlN, is reduced by nonabsorbable antacids. Occasional elevation in serum SGOT, SGPT, or LDH levels is rapidly reversible and not associated with histological evidence of hepatic damage.

Effect of Cholestyramine and Pectin on Induction and Regression of Atherosclerosis in Cholesterol-fed Cockerels

Ruth Pick, Savitri Jain, and Louis N. Katz, Chicago, Illinois

Our studies on different dietary constituents have shown that proteins, carbohydrates, and fats all play a role in the atherogenicity of a cholesterol-containing diet. However, the induction and regression of hypercholesterolemia and coronary atherosclerosis do not always have the same response to dietary manipulations. In the present experiments, cholestyramine and pectin were shown to prevent cholesterol-induced hypercholesterolemia and coronary atherogenesis. However, during regression while on a regular mash diet without cholesterol, addition of cholestyramine had no influence on the rate of regression, while added pectin (5%) retarded the regression rate. The mechanism for this pectin action is not clear. The similarity to findings of low protein levels suggests that pectin both inhibits cholesterol absorption and interferes with protein metabolism.

This latter would also explain the decreased weight gain when pectin was ingested. The low protein effect is obscured during induction because inhibition of cholesterol absorption is dominant. However, during regression, when no cholesterol is added to the diet, the low protein effect emerges. Refined carbohydrates added to a regular high-starch mash diet have no effect on atherogenesis. Experiments with carbohydrates of different composition in a refined semisynthetic diet are in progress.

Effect of Type of Dietary Saturated Fatty Acid on the Production of Endotoxin-initiated Phlebothrombosis in Rat (P)

Serge Renaud and Claude Allard, Montreal, Quebec, Canada

In Holtzman male rats fed for 11 weeks the following hyperlipemic diet: casein 11, cellulose 15, cholesterol 5, fat 31, sodium cholate 2, salt mixture 4, sucrose 23, vitamin mixture 2, water 7 (weight per cent), the intravenous injection of S. *typhosa* lipopolysaccharide (0.6 to 1 mg/kg) initiates the formation of large hepatic vein thrombosis, responsible for multiple hepatic infarcts. According to the dietary fat, the incidence varied from 94% (16/17) with butter, to 53% (8/15) with arachis oil, and to 33% (6/18) with coconut oil. To verify whether the difference in the thrombogenic capabilities of these fats could be related to their saturated fatty acids components, groups of 11 to 18 rats were fed the above diet, containing in the control groups lard (31%) as dietary fat, or in the experimental groups lard (23%) plus 8% of either caprylic, palmitic, stearic, or behenic acid. After six to eight weeks of diet feeding, only the groups with palmitic and stearic acids presented a high incidence of thrombosis as initiated by the endotoxin injection, and their plasma clotting time (siliconized tubes) was lower than in the other groups. The groups fed the palmitic and stearic acids did not exhibit higher serum cholesterol or triglycerides, but showed, as evaluated by paper electrophoresis, a much lower percentage (from 4 to 14%) of serum lipoproteins in the albumin zone (alpha-lipoproteins) than the groups fed the nonthrombogenic fatty acids (caprylic acid 69%, behenic 70%).

Early Spontaneous Coronary Atheroma In Swine

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The incidence and distribution of spontaneous coronary and aortic atherosclerosis was studied in 65 barrows of the Duroc breed, mantained for 162 to 210 days on copper-rich farm rations unsupplemented with fat or cholesterol. Three different types of lesions were found in 27 of the animals. They varied from intimal hyperplasia with acid mucopolysaccharide deposits, particularly hyaluronic acid, chondroitin A and C, and heparitin sulphate (62%); reduplication and fracture of the internal elastic membrane (15%); intimal hyperplasia with neutral and esterified cholesterol deposits (7%); and combined lesions (36%). The number of lesions was significantly higher in the coronary artery, particularly the anterior descending branch (63%), than in either base of aorta (32%) or aortic arch (5%). Fragmentation of the internal elastic membrane did not resemble that found in copper-deficient swine. Gas liquid chromatography showed statistically significant increase in triglyceride and neutral fat of palmitoleic, stearic, and oleic acids. These studies are the first to show a high incidence of spontaneous coronary intimal changes resembling human lesions in farm pigs less than a year old.

Estrogens, an Estrogen Progestin Combination, and Clotting Factors

Roger W. Robinson and Raoul J. LeBeau, Worcester, Massachusetts

Twenty-five student nurses age 18 to 21 were studied with various tests of coagulation during three stages of their menstrual cycle, day 1 to 5, day 10 to 13, and day 18 to 21. The mean prothrombin time was 14 seconds and the thromboplastin generation 5.6 in each observation period. The partial thromboplastin was 48, 48, and 51 seconds, respectively. The prothrombin consumption was 30, 27, and 27 seconds. Platelet adhesiveness varied from 48 and 41 to 45%. No significant change occurred during menstruation, at the estrogen testosterone peak, or in the progestational phase.

Ethynylestradiol was given to 28 women divided into three groups at 0.1 mg, 0.02 mg and 0.01 mg daily for one month. Observations were made during a control period, after one month of therapy, and one month post-treatment control. No changes were recorded in any of the above clotting factors with ethynylestradiol.

Ten mg daily of norethynodrel and ethynylestradiol 3-methyl ether was administered to 25 postmenopausal women. They were examined in the same way. The mean prothombin time was 14, 14, and 14 seconds in the three periods. Thromboplastin generation was 5.1, 4.5, and 4.6 minutes. Partial thromboplastin was 53, 45, and 48 seconds. The prothrombin consumption increased from 38 to 53 seconds ($P > .001$) on treatment and 31 seconds control. The platelet adhesiveness was 56, 56, and 45%, and fibrinogen

224, 215, and 226 mg in the three periods. With this estrogen-progestin combination, a statistically significant increase in prothrombin consumption was observed.

Timing of the Arterial Sounds in Arteriosclerosis and Myocardial Infarction

Simon Rodbard, Duarte, California

The timing of the arterial sounds of sphygmomanometry in the cardiac cycle was used to compare normal subjects with patients with diabetes mellitus and/or myocardial infarction. In normal adults, aged 15 to 80 years, the arterial sounds at diastolic pressure levels appeared at 0.21 ± 0.01 second following the onset of the QRS complex; the sounds at systolic pressures appeared at 0.30 ± 0.02 second. In patients with diabetes mellitus, the diastolic time tended to be early, averaging 0.18 second. Beginning with the seventh decade, the diastolic time appeared as early as 0.12 second in an increasing percentage of apparently normal subjects tested, while the systolic values were as late as 0.50 second. Several males, aged 40 to 50, had very early diastolic times ranging from 0.12 to 0.15 second; these individuals all had histories of myocardial infarction.

At the onset of an acute myocardial infarction, the sounds were delayed about 0.03 second, and the intensities and durations of these sounds were markedly reduced. The timing and intensities of the sounds gradually returned to nearly control values over the course of three weeks. The data indicate that the timing of the arterial sounds may provide an innocuous means for the repetitive testing and identification of certain individuals who have an increased risk of infarction. Cardiovascular dynamics in arteriosclerosis and in acute and chronic myocardial injury may also be analyzed by this means.

Formation of Coprostanyl Esters in Human Feces (P)

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The observation that there are appreciable amounts of sterol esters in feces prompted an investigation to identify the sterols and to study the route of esterification. Accordingly, portions of a fecal suspension were incubated in separate experiments with 7α-^{3}H-cholesteryl palmitate and 1-^{14}C-palmitic acid. It was found that: (1) The major sterol of the ester fraction (about 300 mg) was coprostanol. (2) The quantity of coprostanyl esters increased at least three-fold during the incubation and was approximately equivalent to the decrease in the amount of free coprostanol. (3) A maximum of 0.1% of the radioactivity in 7α-^{3}H-cholesteryl palmitate was present in coprostanyl palmitate at the conclusion of the experiment. (4) About 6% of 1-^{14}C-palmitic acid appeared in coprostanyl esters. (5) From 5 to 7% of the 7α-^{3}H-cholesteryl palmitate was hydrolyzed. Since little of the radioactivity appeared in coprostanyl palmitate during the incubation when large amounts of coprostanyl esters were being produced, it may be concluded that the major route of formation of coprostanyl esters is by esterification of free coprostanol and not by reduction of cholesteryl esters. The data are entirely in accord with the sequence: (1) 7α-^{3}H-cholesteryl palmitate $\rightarrow$ ^{3}H-cholesterol + palmitic acid. (2) ^{3}H-cholesterol $\rightarrow$ ^{3}H-coprostanol. (3) ^{3}H-coprostanol + fatty acids $\rightarrow$ ^{3}H-coprostanyl esters. It is probable that the esterification is carried out by fecal bacteria.

Reduction of the Rapidly Miscible Pool of Cholesterol by Neomycin in Man (P)

Paul Samuel, Charles M. Holtzman, Edward Meilman, and Olya B. Shalchi, New Hyde Park, New York

Five patients received 31 to 43 μc of cholesterol-7α-H^{3} (225 μc/mM) intravenously during control periods. Specific activity of total serum cholesterol was determined serially during the first week and weekly thereafter. Twenty-eight to 59 weeks after injection of the tracer, when no further radioactivity could be detected in serum cholesterol, 2 g of oral neomycin was given daily to four patients. Average total serum cholesterol concentrations were reduced by 20, 21, 26, and 29% respectively in these subjects. The fifth patient, given placebo, had no change in serum cholesterol. After a period of 12 to 26 weeks of neomycin, the intravenous injection of cholesterol-7α-H^{3} (31 to 42 μc) was repeated. The time interval between the two tracer tests was 44 to 76 weeks. The rapidly miscible pool (RMP) of cholesterol was calculated on the regression curve of specific activity during the first six to seven days following each injection of tracer. The size of the RMP was 26.2, 38.9, 44.4 and 44.8 g respectively during control periods, and 16.9, 25.8, 24.1 and 28.2 g respectively following reduction of serum cholesterol by neomycin. The average t½ of the regression of specific activity after one week was 8.1 days during control and 5.4 days during neomycin periods in the four patients. The fifth patient, given placebo, had a RMP of 25.8 g during control and 25.4 g during placebo period, with a t½ of 6.5 and 6.3 days respectively. These results indicate that the oral administration of neomycin reduced the RMP of

cholesterol, which includes serum, red blood cell, and liver cholesterol, by 34 to 45%.

Long-term Reduction of Serum Cholesterol Levels by Small Doses of Neomycin in Patients with Arteriosclerosis

Paul Samuel and Olya B. Shalchi, New Hyde Park, New York

Ten patients were given neomycin orally for periods varying from one to 2.6 years, following control periods of nine to 58 weeks. Serum cholesterol levels were determined at one- to two-week intervals. Following an initial daily oral dose of 2 g of neomycin sulfate, the daily dose was varied between 0.5 and 2 g in the course of the experiment, according to response. Average total serum cholesterol concentrations decreased by 14 to 33% ($P < .001$), the average fall for the group was 22%. Serum cholesterol levels were maintained at the lower plateau as long as the drug was given. In an additional patient, after two months of neomycin administration, there was no change in serum cholesterol concentration and the study was discontinued. Another subject developed severe diarrhea, nausea, and abdominal cramps during the first week of the experiment so that medication was interrupted. No other serious side effects occurred. During the first two weeks of medication, four of ten patients experienced abdominal cramps or diarrhea, which subsided during continued medication. The weight of the patients remained constant and periodic tests for hematopoietic, kidney, and liver functions remained normal. No pathogens were grown from serial stool cultures.

Influence of Free Fatty Acid (FFA) on Glucose Metabolism in Vivo and in Vitro (P)

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Recently we have demonstrated that in healthy dogs intravenously administered sodium octanoate in doses which raise plasma FFA levels decreases plasma glucose concentration. The following studies were performed to elucidate the mechanism by which this eight-carbon fatty acid exerts its effect on glucose metabolism.

Five-hour infusions were administered intravenously to 12 dogs; three received 0.9% saline, three received 2 g % albumin in saline, three received 0.16 M octanoate in saline, and three received albumin plus octanoate in saline at pH 7.4. Glucose-U-C^{14} was injected intravenously at 75-minute intervals, and plasma was analyzed for glucose specific activity, insulin by immunoassay, and for FFA, cholesterol, and triglyceride concentrations. Infusion of 1.5 to 3 mmoles octanoate/kg/hr decreased glucose mass and both rates of glucose appearance (primarily of hepatic origin) and disappearance (tissue uptake), while the glucose space and plasma insulin did not change. Cholesterol and triglyceride concentrations were unaltered by octanoate, but were decreased by albumin.

In vitro studies with perfused hearts from fed rats demonstrated that both 0.6 and 3.0 mM octanoate decreased uptake and altered the pattern of utilization of 5 mM glucose-U-C^{14} in the absence or presence of 0.1 unit/ml insulin. These effects on uptake and utilization were greater at the higher concentration of octanoate.

It is concluded that octanoate infusion lowers plasma glucose concentration by decreasing hepatic glucose output without detectable change in plasma insulin concentration of peripheral blood. The decreased rate of glucose disappearance may be explained by a direct effect of octanoate on glucose uptake by muscle.

Fibrinolytic Activity in the Tissues of Patients Dying of Acute Myocardial Infarction

Herschel Sandberg, Etienne Van der Stichele, Leonard J. Feinberg, Samuel Bellet, and Eileen Mazer, Philadelphia, Pennsylvania

The tissue fibrinolytic activity of 13 patients dying of acute myocardial infarction was compared with that of 36 subjects dying of other causes by preparing, from fresh necropsy material, thiocyanate extracts of aorta, lung, pancreas, heart, adrenal, spleen, kidney, prostate, and liver. These extracts were processed in a manner described by Astrup and Albrechtsen, then pipetted in duplicate onto unheated bovine fibrin plates. Pig heart controls were pipetted on the opposite side of the plates. After an 18-hour incubation period, the areas of the zones of lysis were determined. The fibrinolytic activity was expressed as the ratio of the area of the zones of lysis produced by the organ extract, to the area of the zones of lysis produced by the pig heart control. In the patients dying of acute myocardial infarction, every organ extract studied, except the liver, showed greater fibrinolytic activity than the homologous organ extract of the remaining subjects: For lung, pancreas, and adrenal, $P < 0.001$; for aorta, heart, and kidney, $0.001 < P < 0.01$; for prostate and spleen, $0.02 < P < 0.05$. The two liver extracts showed no statistically significant differences. When the organ extracts were pipetted onto heated agar-fibrin plates, only spleen showed zones of lysis. These results give added significance to the increased urokinase excretion reported in subjects with acute myocardial infarction by Smyrniotis

et al., since both findings may represent attempts by the organism to compensate for the infarction by mobilizing tissue activator of plasminogen.

Aspects of the Conversion of the HDL_2 and HDL_3 Subclasses of Human Serum High-density Lipoprotein (HDL) (P)

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In an attempt to give a molecular basis for the conversion of the HDL_2 ($1.063 < \rho < 1.120$) and HDL_3 ($1.120 < \rho < 1.21$) subclasses of human serum HDL, comparative physical and chemical parameters were determined. In accord with previous data, the molecular weight of HDL_2 was about twice ($3.6 \times 10^5 \pm 2.1 \times 10^4$) that of HDL_3 ($1.7 \times 10^5 \pm 1.2 \times 10^4$). Differences were also noted in intrinsic viscosity, partial specific volume and frictional ratio. After delipidation with ethanoldiethyl ether at −10 C, the lipid-poor residues had a tendency to polymerize readily, and could be reduced into subunits of an average molecular weight of 2.0×10^4 Amino acid and carbohydrate distribution, NH_2- and COOH-terminals were identical with those of the parent molecules. From the data on molecular weight and protein mass, it was estimated that HDL_2 and HDL_3 contain an average of seven and five subunits respectively. The findings, and the known difference in lipid content of the two HDL subclasses, suggest that HDL_3 derives from HDL_2 by a process of lipid removal and concomitant release of a portion of its protein moiety. In support of this hypothesis were the data showing that a lipid-poor, very high-density lipoprotein (VHDL) is present in $\rho >$ 1.21 bottom residues and in fresh sera. Degree of lipidation of HDL may thus depend, in part, upon number and degree of polymerization of its peptide subunits. Since the latter can undergo relipidation, the occurrence of an "HDL cycle" ($HDL_2 \rightarrow HDL_3 \rightarrow VHDL \rightarrow HDL_2$) may be postulated.

Mechanism of Activation of Platelet Factor Three (P)

Edward M. Scolnick, Daniel Deykin, Carole R. Pritzker, and Thomas P. Ashford, Boston, Massachusetts

Early stages of thrombus formation in flowing blood are postulated to involve aggregation of platelets followed by activation of platelet factor three (PF3), a phospholipid acceleratory to the intrinsic coagulation system. The activation of PF3 was investigated in an in vitro system in which platelets were aggregated by adenosine diphosphate (ADP), by thrombin, and by ADP and thrombin sequentially. ADP-induced aggregation did not stimulate PF3, and electron micrographs of the aggregates revealed normal intracellular architecture. Thrombin treatment resulted in measurable PF3, and slight intracellular changes were discernible. ADP followed by thrombin stimulated PF3 five- to eightfold over that observed with thrombin alone. Electron micrographs revealed large, tightly packed platelet clumps with intact external membranes but with striking intracellular cytologic alterations. Following stimulation by ADP and thrombin, the platelet-free reaction medium was assayed for PF3 and phospholipid. No PF3 was found in the medium and colorimetric assays revealed no additional phospholipid. To detect smaller amounts of phospholipid that might have been released, platelet lipids were labeled with acetate-1-C^{14}. During PF3 activation, no release of phospholipid radioactivity was detected, although significant intracellular labeling of phospholipid had occurred. Combined morphologic and biochemical evidence thus indicates that activation of PF3 can occur by the sequential action of ADP and thrombin, and that this process does not involve physical release of platelet phospholipid.

Difference in Coronary and Cerebral Atherosclerosis in New Yorkers: Apparent Independence from Medial Thickness, Fatty Acid Patterns and Blood Constituents (P)

R. Foster Scott, Assaad S. Daoud, Bernard Wortman† and Ethel S. Morrison, Albany, New York

In 138 males the amount of atherosclerosis as measured by wall thickness was greater in coronary than in basilar and middle cerebral arteries (0.41 vs 0.27 mm). In coronary and cerebral arteries of 16 males, age 60 to 69 years, (analyzed chemically), light microscopy measurements showed that the difference resulted from intimal thickening (intima 0.74vs.0.17 r mm, media 0.18 vs 0.15 mm). For chemical analysis of coronary arteries having more nearly the same amount of atherosclerosis as in cerebral arteries 60 to 69 years old, we arbitrarily selected 11 coronaries from a 30 to 39 age group.

In the 60- to 69-year group, cholesterol and triglyceride (mg/g dry weight) were significantly higher in coronary than cerebral arteries (69 vs 23, and 33 vs 11); amount of phospholipid was similar. Relative per cent of cholesterol and triglyceride fatty acids of these arteries showed only small differences consistent with differences in stage of the disease. Lipid concentration in the 30 to 39 coronary and 60 to 69 cerebral

arteries showed higher triglyceride and cholesterol levels in coronary arteries. Concentration of cells/g of defatted artery (approximated by DNA levels) was roughly inversely proportional to amount of lipid present, being in young coronaries, old cerebrals, and old coronaries 13×10^8, 12×10^8, and 7×10^8. Thus, although other interpretations are possible, differences in amount of atherosclerosis in coronary and cerebral arteries appear independent of medial thickness, arterial fatty acid patterns, or blood constituents. This suggests that there may be basic differences in metabolism of the two arterial walls, related to hemodynamic, structural or other factors.

Metabolism of Δ^4-Cholestenone in Vitro (P)

Sarah Shefer, Susan Hauser, and Erwin H. Mosbach, New York, New York

The ready conversion of Δ^4-cholestenone to 5α-cholestan-3β-ol (DHC) in mammalian tissues suggests that this Δ^4-3-ketosterol lies on the metabolic pathway leading from cholesterol to DHC.

The transformation of Δ^4-cholestenone to DHC proceeds via 5α-cholestan-3-one as an intermediate; the enzyme systems catalyzing these reactions have not been studied in detail. We have now found that the microsomal fraction of rat liver homogenate contains a Δ^4-3-ketosterol reductase which converts Δ^4-cholestenone to 5α-cholestan-3-one. The microsomes do not catalyze the further transformation of 5α-cholestan-3-one to DHC. The properties of the Δ^4-cholestenone reductase resemble those of the known microsomal *steroid* 5α-reductases in certain respects (NADPH requirement, pH optimum, sex difference) but differ in others (the *sterol* reductase is inactive when NADH is used as the electron donor).

The enzymatic reduction of Δ^4-cholestenone was strongly inhibited by Δ^4-androsten-3, 17-dione and testosterone, less so by the reaction product (5α-cholestan-3-one) and by 5α-androstan-3, 17-dione. In contrast, the microsomal Δ^4-3-keto*steroid* 5α-reductase (acting upon Δ^4-androsten-3, 17-dione) was not inhibited by 5α-androstan-3, 17-dione, and its activity was strongly stimulated in the presence of 3-keto*sterols*.

Prevention of Edematous Arterial Reaction and Atherosclerosis of Cholesterol-fed Rabbits by Anti-bradykinin Agents

Takio Shimamoto, Fujio Numano, Masayoshi Kubota, and Tsutomu Fujita, Tokyo, Japan

Edematous arterial reaction is an immediate and general reaction of arterial walls of animals to the stresses such as administration of atherogenic substances or traumatization. The reaction consists of a microscopic swelling of arterial wall due to the accumulation of serous material in the amorphous extracellular spaces of intimal and medial layers, showing a close similarity to "Das initiale fettfreie Ödem," the hypothetical initial stage of human atherosclerosis of German school.

In an attempt to prevent the reaction, ergotamine tartarte, atropin, pyribenzamine, dexamethasone, etc. were employed in relatively large doses without effect, while the following substances were effective:

(1) Trasylol(300 U/kg iv): a bradykinin-forming (polyvalent proteolytic) enzyme-inhibiting substance.

(2) Anti-bradykinin agents in veins: acetylsalycilic acid (50 mg/kg p.o.), nialamide (50 mg/kg p.o.), cyproheptadine (5 mg/kg p.o.) and pyridinolcarbamate (1 mg/kg p.o.).

The atheromatous changes in cholesterol-fed rabbits were slightly inhibited by nialamide (10 mg/kg/day p.o.) and cyproheptadine (5 mg/kg/day p.o.) and markedly inhibited by pyridinolcarbamate (5 mg/kg/day p.o.), showing a characteristic tendency of fibrous healing. Pyridinolcarbamate not only minimized markedly the atheromatous changes and accumulation of cholesterol in arterial walls ($P < 0.01$), but also prevented remarkably the formation of atheroma, its fatty degeneration, and necrosis formation ($P < 0.01$) of animals kept on cholesterol diet for 15 weeks, with the high serum cholesterol level amounting $1{,}735 \pm 169$ mg/kg during the last five weeks of experiment.

Studies on the Metabolism and Fate of Intestinal Cholesterol

Harbhajan S. Sodhi, Victoria Berger, Elizabeth A. Swyryd, and R. Gordon Gould, Palo Alto, California

Cholesterol synthesis was shown by Taylor and Gould to proceed rapidly in intestine of cholesterol-fed as well as normal animals. To determine how rapidly cholesterol synthesized in intestine appears in plasma and liver, we injected acetate-C^{14} into control and cholesterol-fed rats and followed the specific activity of free cholesterol in all three tissues. In both groups, the initial half time of disappearance of free cholesterol-C^{14} from intestine was about one day. Liver and plasma values were as high as intestine in the control rats, and the rates of disappearance of all three were approximately the same. In the cholesterol-fed rats, liver and plasma values were low at four hours and did not show any increase during the subsequent five days, by which time the values were approximately equal in all three tissues in both groups. Cholesterol-H^3 was fed and acetate-1-C^{14} injected into rats previously

fed inert cholesterol; one day later the S.A. of free cholesterol-H^3 was as high in liver as in intestine whereas cholesterol-C^{14} S.A. was much lower in liver than in intestine. This suggests that dietary cholesterol may be able to pass through the intestine without equilibrating completely with the newly synthesized cholesterol present in intestine.

Separation of villi from the crypt cell fraction by the method of Dietschy and Siperstein 90 minutes after the injection of acetate-C^{14} gave higher S.A. values of free cholesterol in villi than in the crypt fraction. Fed cholesterol-H^3 was similarly distributed in both fractions four hours after administration.

Relationship Between Severity of Hypertensive Complications and the Level of Arterial Blood Pressure in Essential Hypertension

Maurice Sokolow, David Werdegar, Herbert Kain, and Allen Hinman, San Francisco, California

The severity of hypertensive complications in 124 patients with essential hypertension, who were not under treatment, was analyzed in relation to their average office or casual blood pressure levels and measurements of their blood pressure obtained with a portable, semiautomatic recorder. The blood pressure of each patient was measured with the portable recorder every half-hour, during normal daytime activity, for two to three consecutive days. The overall severity of hypertensive complications was graded from zero to four according to a schema based on the degree of abnormality noted on fundoscopic examination, electrocardiogram, and chest X-ray determination of heart size. The analyses disclosed highly significant relationships between both the mean systolic and diastolic portable recorder pressures and the presence and severity of hypertensive complications. The relationships were quantitative: the higher the pressure, the greater the severity of each hypertensive complication and of overall severity. There was no correlation between the variability of portably recorded pressures and severity. Significant relationships were also noted between the average casual systolic and diastolic pressures and the severity of hypertensive complications; however, mean portably recorded pressures were much more highly correlated. The portable recorder pressure measurements explained some of the apparent discrepancies between the casual blood pressure levels and the severity of complications encountered clinically in individual cases. Revealing details of stepwise multiple correlations and other statistical analyses of the data will be presented.

Influence of Norethnodrel with Mestranol on Atherogenesis in Rabbits

David M. Spain and Ascher L. Mestel, Brooklyn, New York

A previous study noted that pregnancy afforded rabbits on a cholesterol-supplemented diet partial protection from atheroma. Others noted that norethnodrel with mestranol altered the media of rabbit aortae with changes similar to those occurring during pregnancy. In order to determine whether the previously noted anti-atherogenic action of pregnancy in rabbits might be related to these medial alterations, a group of white New Zealand rabbits on cholesterol-supplemented diet were treated with norethnodrel with mestranol. At the end of eight weeks, the aortae of the treated rabbits revealed distinctly less atheroma than did the controls. We could not confirm the vascular structural alterations previously reported. To determine whether this anti-atherogenic effect was entirely due to the estrogenic activity of the above compound, four groups of rabbits on cholesterol-supplemented diets were treated as follows: a control group; a group receiving norethnodrel with mestranol; a group receiving conjugated estrogens; and a group receiving progesterone. After eight weeks there was less atheroma in the aortae of the three treated groups than in the controls. The progesterone-treated group revealed less atheroma than the controls, but more than the other two groups. It appears that the anti-atherogenic effect of norethnodrel with mestranol cannot be explained solely by its estrogenic activity, and that progesterone may contribute to this effect. Further studies of the possible anti-atherogenic effect of progesterone in rabbits are warranted.

Mechanism and Kinetics of Free Fatty Acid (FFA) Uptake and Utilization (P)

Arthur A. Spector and Daniel Steinberg, Bethesda, Maryland

Suspensions of Ehrlich ascites tumor cells can be exposed uniformly to various media, and uptake and utilization of labeled FFA can be exactly quantified relative to number of cells exposed. Immediately on exposure to FFA-albumin, there is a rapid transfer of FFA from albumin to the cell. An equilibrium cellular FFA concentration is reached within one minute, the magnitude depending on the molar ratio of FFA to albumin ($\bar{\nu}$), independent of *total* FFA concentration in the medium. This cellular FFA pool is maintained at a stable level during continued incubation, while the amounts incorporated into esters and oxidized to $C^{14}O_2$ increase pro-

gressively. Studies of cells exposed to labeled FFA and reincubated in buffer suggest that medium FFA pass through this tissue FFA pool prior to utilization. The rate of FFA utilization depended on the equilibrium cellular FFA concentration which, in turn, is determined by extracellular $\bar{\nu}$. Over the range of $\bar{\nu}$ values ordinarily found in human plasma, the rate of FFA utilization increased linearly with $\bar{\nu}$. Lauric, palmitic, stearic, oleic, and linoleic acid utilization were qualitatively similar. While the equilibrium FFA uptake was larger with saturated FFA, the rate of utilization relative to the equilibrium cellular FFA content was greater for unsaturated FFA. Glucose increased total FFA uptake without altering the cellular equilibrium FFA content. Thus, the rate of FFA utilization is controlled both by the magnitude of the steady state cellular FFA pool (a function of $\bar{\nu}$) and by the metabolic factors affecting the turnover rate of this pool.

Immunofluorescent and Histological Study of Dacron Vascular Prostheses in Man (P)

Minoru Suzuki, Robert M. O'Neal, George L. Jordan, Jr., and Michael E. DeBakey, Houston, Texas

The inner surface of Dacron vascular prostheses surgically grafted in man is covered with a thin lining of fibrin in uncomplicated cases. Dacron prostheses surgically removed from patients who had previously undergone surgical correction of major arterial disease have been studied by light and electron microscopy. The light microscopical examination was aided by the use of the immunofluorescent technique using fluorescein isothiocyanate-conjugated rabbit antihuman fibrin and by various special stains. Although fibrosis and foreign-body reaction were commonly noted near suture line, inner linings of the excised prostheses at 2 cm from the suture line were largely acellular and usually devoid of endothelium. Electron microscopy revealed coarse fibrin strands near the surface, and fine fibrillar material mixed with cell debris in the deeper areas of the inner lining of the prosthesis. Immunofluorescent preparations revealed brightly fluorescing strands of fibrin on luminal surface, but weakly fluorescing fibrin in deep portion of the inner layer. Interstices of the prostheses were also filled with fibrin, but foreign-body reaction was rare. The results suggest that the deposition of successive layers of fibrin takes place on the inner surface of the prosthesis. The continuous deposition and lysis of fibrin on the innermost surface of prostheses may be the principal mechanism by which patency of the prosthetic lumen is maintained.

Blood Pressure, Relative Body Weight, and Height in Sedentary and Physically Active Railroad Employees at Time of Employment and at Ages Forty to Fifty Nine

Henry L. Taylor, R. W. Parlin, Henry W. Blackburn, Thomas C. Puchner, and Ancel B. Keys, Minneapolis, Minnesota

Evidence for occupational selection carrying with it differential distribution of coronary heart disease risk factors was sought in preemployment examinations and early employment health records of switchmen and clerks who had been examined in a survey of these occupations in 1958-59. Systolic and diastolic blood pressures and age at time of preemployment examinations were obtained on 417 switchmen and 297 clerks who were 40 to 59 in 1958-59. The age range at entry to employment was 17 to 49 in both groups and the median in both groups was in the 30- to 34-year age group. Height, weight, and age data at preemployment examination were found in 381 clerks and 405 switchmen who had been examined in 1958-59. In this group, clerks' median age at entry into the railroad industry was in the 20- to 24-year age class. The median age at occupational entry for the switchmen studied for height and weight was in the 30- to 34-year age group.

Comparisons were made between clerks and switchmen for all variables at the time of employment and at the examination in 1958-59. Age-adjusted quartiles and age-adjusted cumulative frequencies were constructed and used to look for differences between switchmen and clerks at both initial employment and at the time of the 1958-59 examination. No differences were found in height, relative body weight (1912 actuarial standards), systolic or diastolic blood pressure between switchmen and clerks at either time of employment or at examination at age 40 to 59. The data offer no evidence of selection in terms of these variables.

Study of Basilar Gangliar Vessels in Human Brain by Tridimensional Microscopy after Injection and Clearing

Henri C. Theodore, Jerome G. Brown, Meyer Brown, and C. Bruce Taylor, Evanston, Illinois

The cerebral arteries were injected selectively with special attention given to the penetrating branches supplying the basilar ganglia. Varied colored latex suspensions were injected. Brains were fixed, sliced, and cleared following the Spalteholtz method, and the vessels were studied with a dissecting microscope. This method allows quick identification of distortions along the course of the vessels and clear demonstration in tri-

dimensional view of anastomoses, if present. Areas showing gross abnormalities were resected for histological sections.

The following parameters are being studied in the basilar gangliar area, which is the principal site of cerebral thrombosis, infarction and hemorrhage: (1) abnormalities of vessels that precede thrombosis of hemorrhage; (2) evaluation of anastomoses between individual penetrating lenticulostriate arteries, and (3) anastomoses from subcortical and cortical vessels to vessels in the basilar ganglia. (These have been demonstrated in some cases.) The presence or absence of these anastomoses and their relationship to ages of individuals is of considerable importance in the genesis of cerebral vascular accidents and infarction in the basilar gangliar areas.

Ecology of Hypertensive Arteriolar Hyalinosis

Richard E. Tracy and Victoria Schauf, Chicago, Illinois

Renal arteriolar hyalinois (RAH) has a strong correlation with risk of dying from heart attack or stroke, and 1,628 suitable autopsies at the University of Chicago Clinics were reviewed. In general, at all ages RAH was more frequent in Negroes than whites of both sexes, and more common in males than females of both races. The income and population density of each patient's home neighborhood was taken from 1960 U. S. Census averages, with a breakdown of Chicago into 935 census tracts. Age-adjusted disease rates were highest in the very poorest and very richest sections of town, and lowest in the middle-income tracts. These trends were true of both races and both sexes. This U-shaped relationship of disease risk to income appeared to be in part associated with physical crowding of the populations in the low income areas, especially among Negroes. The lower average socioeconomic level of the Negro seemed quantiatively sufficient to explain the higher average disease rate in that race. When the study was repeated on only those cases that did *not* die of heart attack or stroke (i.e. those cases who had RAH only *incidentally*), these trends persisted, suggesting that sampling bias probably does not explain the correlations.

Studies of Vascular Calcification and Elastic Tissue Density by Means of Ultra-soft X-Rays (X-Ray Microscopy)

Theodore T. Tsaltas, Philadelphia, Pennsylvania

Ultra-soft x-rays have been employed for the investigation of the early calcification found in atherosclerotic lesions and the medial calcification of blood vessels. X-rays were used because the existing histochemical methods for Ca are highly unreliable and positive results are so diffuse that exact localization of small Ca deposits is quite inaccurate. The wave length of the x-rays used was from 4 to 40 A with the major energy peak (80%) corresponding to the Ka line, specific for the demonstration of Ca. Tissues fixed in formaldehyde and sectioned at 3 to 5 μ were used for all x-ray experiments. These constitute major advantages since no special handling of tissues is required. Other advantages of the method are the low cost and simplicity of the equipment, and the preservation of the tissue used for x-rays for further microchemical analysis, or other histochemical examination. Serial sections of aortic tissue were examined by ultra-soft x-rays or stained with Van Cossa, Alizarine, and H + E. The x-rays proved to be far more accurate than the histochemical methods, and Ca could be localized with precision in situ.

The relative density of elastic tissue in blood vessel walls was also investigated by x-ray microscopy. The elastic tissue was found by x-rays to be much denser than smooth muscle or fibrous tissue. This resulted in an outstanding demonstration of fine details of elastic tissue elements.

Effect of Cholesterol-Feeding on Aortic Transplants into the Anterior Chamber of Rabbits' Eyes

Arthur F. Whereat, Robert A. Rubinstein, and Iraj H. Nazarian, Philadelphia, Pennsylvania

Aortic tissue was removed from donor rabbits and placed in the anterior chamber of the eyes of recipients (technique of Higginbotham). Chemical and histological changes in the transplant and the eyes were observed under an atherogenic stimulus.

There were three groups of animals. Group A: the anterior chamber of one eye received an aortic transplant and the group was fed the usual rabbit pellets. Group B: one eye received a similar transplant and this group was fed a 2% cholesterol (atherogenic) diet. Group C: one eye received a sheet of silicon equal in size to the aortic transplants and this group received an atherogenic diet.

Serial observations were made of morphological changes in the eyes and changes in cholesterol content of blood, aqueous and conjunctive. At the conclusion of the feeding period, histological and chemical analyses were made on individual eye structures and the aortic transplants.

In groups B and C the cholesterol content of the blood, iris, ciliary body, and the recipient's own aorta rose 90- to 100-fold, and the latter tissues contained numerous lesions. The cholesterol content of the aqueous rose 15- to 20-fold

and the aortic transplants showed an increase of the same magnitude.

The aorta, regardless of the location, retained the ability to accumulate cholesterol. The accumulation was similar in magnitude to the percentage rise of cholesterol content of the fluid with which the aorta was in contact. In the rabbit, the iris and ciliary body accumulate cholesterol and develop lesions morphologically similar to those in the in situ aorta.

Long-Term Effect of Heparin on Patients with Coronary Artery Disease and Associated Hyperlipemia

Asher Woldow and Harry Goldberg, Philadelphia, Pennsylvania

Triglyceride values and turbidity levels have frequently been reported as abnormally elevated in patients with coronary artery disease. Following a fat-load meal, the values remain higher for a long time in patients with coronary artery disease. These postprandial levels are significant, as fasting levels exist only for a short time in a 24-hour period.

Maintenance of lower fasting levels with drugs has been generally discouraging.

Heparin, when given in an attempt to prevent postprandial lipemia, is followed by rebound lipemia more severe than when no heparin was used. We believe this may be due to heparin effect on gastrointestinal absorption delaying fat absorption. Keeping the heparin level constant with four-hour injection intervals can prevent the rebound from occurring.

Treatment of 18 patients on long-term basis (one to 18 months) with heparin injections every 12 hours has been under study. In most cases, the fasting levels were not reduced significantly, but in the hyperlipemic group (six patients), a significant reduction was found five hours postprandially. In the normolipemic group (12 patients), this was not noted.

Our results suggest that long-term heparin does not significantly alter the fasting levels of either the normo- or hyperlipemic groups but may be of significant therapeutic value in those patients who show a marked five-hour lipemia.

Ultrastructure of Aortae at Early Stage of Calcification on Epinephrine-Injected Rabbits

Shiu Yeh Yu, St. Louis, Missouri

In the previous experiments in epinephrine-induced aortic calcification, 75% of the rabbits developed calcified lesion during the sixth week after five weeks of daily single injection of epinephrine. In the present study, the aortae were obtained at the fifth week after four weeks of daily single injections. On chemical assay, a slight increase of calcium in the aortic elastin was observed. Morphologically, a diffuse arteriosclerotic lesion without apparent calcification was found in the areas of arch and ascending aorta. Acidic mucopolysaccharides were seen in interspace between disorganized and polarized smooth muscle cells and elastic lamellae. In the subendothelial space, proliferating fibroblasts and synthesis of collagen and elastic fiber were seen. In the medial portion adjacent to internal elastic lamella, alteration of smooth muscle cells was seen; vacuoization, swelling of mitochondria, and an accumulation of glycogen particles near endoplasmic reticulum were observed. It was noteworthy that the cytoplasmic membrane of the smooth muscle cells at this area became fibrilar, replacing the envelope-like membrane normal cells. The anchorage points between smooth muscle cells and elastic fiber diminished and were replaced by collagen and poorly oriented elastic fiber. The spherical particles of calcium compound nucleated on the elastic fiber at these disrupted points. Also, early calcification may take place on elastic fiber in the subendothelial space. An increase in the amorphorus mass of collagen-elastic fiber material between smooth muscle cells occurred concomitantly with the decrease in total mass of smooth muscle cells. Disruption of tissue organization led to acceleration of abnormal synthesis activity of the connective tissue elements at local areas in the aorta.

Determination of Myocardial Alterations at Autopsy in the Absence of Gross and Microscopic Changes (P)

Frederick T. Zugibe, Paul Bell, Thomas L. Conley, and Mary S. Standish, Pittsburgh, Pennsylvania

The diagnosis of myocardial infarction at autopsy can only be ascertained with certainty in the presence of gross and microscopic changes. If a frank obstruction of the coronary arteries is not present in a patient living less than 12 to 18 hours, the diagnosis can only be speculative based on the clinical findings. A simple method has been standardized for biochemically determining myocardial alterations within one hour after death. The method was first tested on a large series of dogs whose circumflex coronary arteries were ligated and the animals sacrificed at various intervals from five minutes to 24 hours. Myocardium from control areas and areas supplied by the circumflex were analyzed for Na, K, GOT, GPT, and LDH. A significant decrease in the K to Na ratio as compared to the control was found as soon as ten minutes after ligation, GOT and GPT loss after 30 to 60 minutes, and LDH

loss after 60 to 90 minutes. The Na to K ratio was selected for routine use since it afforded the most consistent results, displayed the earliest change, was resistant to autolytic change, required the smallest amount of sample, and was simplest to execute. The other procedures were utilized as additional controls. This method was then applied to a large series of human myocardial samples from all cases brought to autopsy without knowledge of the postmortem or clinical findings. The biochemical data was in complete agreement with the postmortem and clinical data. The results of these studies will be discussed in detail.

Thrombus Growth Under the Influence of Warfarin and After Abrupt Reversal of Its Effects

Andrew J. Zweifler, Ann Arbor, Michigan

Recent evidence has suggested that mild depression of prothrombin activity may encourage thrombus formation, and it has long been held that a similar effect occurs after sudden withdrawal of anticoagulant therapy. This report assesses the effect of varying degrees of prothrombin depression and abrupt correction of hypoprothombinemia with large doses of vitamin K_1 on thrombus growth in vivo. Thrombi were initiated electrically and allowed to propagate for 6½ hours in the common carotid artery of the rabbit. In 20 control animals, weights of thrombi produced in one carotid were compared to those in the other on a subsequent day. Second carotid thrombus weight was consistently greater than first (mean increase + 22.0%). Thirty-seven animals were treated for ten to 30 days with IM warfarin. In rabbits with prothrombin concentrations (Quick test) in the 15 to 30% or $>30\%$ ranges, weights of second carotid thrombi were also greater than first (+10.9 and +10.1% respectively). In animals with prothrombin concentration $>15\%$, however, second carotid thrombi were significantly decreased in weight (mean change −20.3%). Eighteen animals were treated with warfarin IM for two weeks and then given 50 mg vitamin K_1 iv. Thrombus weights two and five days after K_1 in these animals did not differ from control values. These results reveal that warfarin therapy has no influence on thrombus growth when prothrombin activity is $>15\%$. Specifically, no thrombophilia was observed with mild degrees of prothrombin depression. Rebound hypercoagulability was not found after abrupt correction of hypoprothrombinemia with large doses of vitamin K_1.

AMERICAN HEART ASSOCIATION

38th SCIENTIFIC SESSIONS

BAL HARBOUR, MIAMI BEACH, FLORIDA

OCTOBER 15-17, 1965

ABSTRACTS

Listed alphabetically by first author

(P) *Papers presented at the Scientific Sessions*

* *Career Investigator, American Heart Association, 1964-1965*

† *Established Investigator, American Heart Association, 1964-1965*

‡ *Research Fellow, American Heart Association, 1964-1965*

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AMERICAN HEART ASSOCIATION
38TH SCIENTIFIC SESSIONS
ABSTRACTS

LEWIS A. CONNER MEMORIAL LECTURE

Major Functions of the Pulmonary Circulation

Julius H. Comroe, Jr., M.D.

The pulmonary circulation has many functions: (1) It is essential for gas exchange; (2) it, with the left atrium, is a reservoir for the left ventricle; (3) it supplies blood essential for the nutrition of the alveoli and alveolar ducts; (4) it is a filter to remove particles in the mixed venous blood; and (5) it can remove fluid present in the alveoli.

Gas Exchange. Local decrease in alveolar O_2 tension can cause local pulmonary vasoconstriction, augmented by increased CO_2 tension, and local pulmonary vascular occlusion can cause local narrowing of airways (Staub; Severinghaus). These mechanisms for vasoconstriction and bronchoconstriction may provide better matching of air and blood in the alveoli; inspired air is directed to regions with good blood flow and blood is directed to regions with good ventilation. Systemic arterial hypoxemia causes generalized pulmonary arteriolar constriction. This is a reflex response initiated in peripheral chemoreceptors (in the dog, the aortic body); it serves no useful purpose in the adult and it may be a carry-over from the fetus, in which anoxemia increases pulmonary vascular resistance and so directs blood away from the pulmonary circulation through the ductus arteriosus and toward the placenta.

Nutrition. The pulmonary circulation is not merely a set of pipes to conduct blood to and from the alveolar capillaries; it is normally essential for the nutrition of the alveolar walls, including alveolar cells and alveolar ducts. The alveolar cells have one known important function: their lamellar inclusion bodies appear to contain a remarkable surfactant (dipalmitoyl lecithin?) that, when layered over the alveolar walls, prevents their collapse. Occlusion of a branch of the pulmonary artery leads to the loss or inactivation of pulmonary surfactant and to atelectasis in the starved area; this process is accelerated if the alveolar capillaries become leaky, because of poor nutrition, and permit plasma, and its fibrinogen, to enter alveolar spaces (Tooley; Clements; Abrams and Taylor). Atelectasis can be reversed if pulmonary blood flow is reestablished or if the bronchial arteries supply blood to the alveolar capillaries. Respiratory distress syndrome in the newborn may be caused or aggravated by pulmonary vasoconstriction and pulmonary ischemia and may be relieved by vasodilators, which improve nutrition (Chu and associates).

Filtration. Although usually regarded as a pulmonary disorder or dysfunction (pulmonary embolism), the removal of particles from mixed venous blood is an important *function* of the pulmonary circulation. Emboli can provoke local and systemic effects, the nature of which depends on the type of emboli, their number, and site of impaction. For example, iodinated poppyseed oil, introduced during lymphangiography, blocks only fine pulmonary vessels (capillaries or precapillaries); although it decreases pulmonary diffusing capacity and pulmonary capillary blood volume, it produces few other measurable sequelae (Gold and associates). At other sites, emboli may initiate bronchoconstriction and possibly reflexes affecting respiration and circulation (Nadel and associates).

GEORGE E. BROWN MEMORIAL LECTURE

Interarterial Shunts in the Cerebral Circulation

James F. Toole, M.D.

In the normal person, there is extensive redistribution of blood within the brain, even though total cerebral flow remains relatively constant. Evidence suggests that this regional autoregulation takes place mainly through leptomeningeal anastomoses on the brain convexity. The circle of Willis at its base acts as a potential communication between the two carotid and the vertebral-basilar systems but the three cerebral circulations seem to function rather independently of one another in the normal base-line state. Under pathological conditions, particularly in obstructive arterial disease, voluminous shunts may develop, both in these pathways and in the cervical portions of the aortocranial arteries. A most important siphoning may take place in patients who have lesions of their innominate or subclavian arteries in the thorax. These occur in such a fashion that the patient may be harmed by his own collateral circulation (the subclavian steal syndrome).

Only a hint of the dynamics of these circulations has been revealed by rapid serial angiography. It is evident that change in the position of the head upon the neck and of the arms in relationship to the neck may alter blood flow through the arteries supplying the brain. Arm exercise, in-

halation of high concentrations of oxygen and carbon dioxide and change of systemic blood pressure may all affect these shunts. The above-mentioned data will be discussed in detail and suggestions made for management of patients with clinical abnormalities arising from these shunts. Avenues for further investigation will be proposed.

Hemodynamic Effects of Activation Order in Premature Beats

J. A. Abildskov, Robert H. Eich, Kay Millar, and Harold Smulyan, Syracuse, New York

The effects of regular ventricular stimulation and of premature ventricular beats on ventricular pressure appear to conflict. Only small differences of pressure occur with regular stimulation from various sites. This suggests that variations of activation sequence are of minor functional importance when the conduction system is intact. By contrast, premature ventricular contractions (PVC's) produce strikingly lower pressure (expressed as percentage of the preceding beat) in the ventricle in which the contraction originates. This has been attributed to more nearly normal activation in the contralateral ventricle.

In this study, PVC's scanning the cardiac cycle were delivered to multiple ventricular sites in four open-chested dogs in which the sinus node had been crushed and the atrium driven regularly. Peak pressure plotted versus stimulus time confirmed a greater percentage pressure fall in stimulated than in opposite ventricle. However, the time of onset of pressure rise was always later in the contralateral ventricle, allowing more time for muscle recovery and ventricular filling. When this factor was taken into account by plotting pressure versus time of onset of pressure rise, with each ventricle considered independently, differences of pressure related to stimulus site were minimized.

Of the four animals, two showed no difference of left ventricular (LV) pressure due to site of stimulation, and two showed no differences in right ventricular (RV) pressure. In two experiments, LV difference of the order of 10%, and in two experiments RV differences of 15%, occurred. These observations are comparable with those during continuous ventricular drive.

Carotid Artery Pressure Tracing in the Evaluation of the Effect of Digitalis on the Left Ventricle

Felix Ades and Walter H. Abelmann, Boston, Massachusetts

In view of the need for bedside assessment of digitalis action, the effects of ouabain (0.4 to 0.6 mg) upon the externally recorded carotid pulse of 13 patients with acquired heart disease (four in failure) were studied.

Stroke power index (SPI) increased in ten, diminished in one (J. B.), and did not vary in two; its mean value for the group increased by 19.2% ($P < 0.001$). The interval between the electrocardiographic Q and the carotid upstroke (pre-ejection time) diminished in nine and did not vary appreciably in four cases; its mean value fell from 0.140 to 0.127 second ($P < 0.001$). Ejection index (Weissler) decreased in eight cases, did not vary appreciably in four, and increased in one (J. B.); it reflected the increase in the mean rate of left ventricular ejection well, but reflected changes in SPI less accurately. Its mean value decreased from 0.404 to 0.387 second ($P < 0.025$).

The maximal rate of pressure rise (D_p/D_t) of the carotid upstroke, expressed in mm Hg by calibration with simultaneous direct brachial artery tracing, increased in all but one patient (J. B.). In 11 cases, both D_p/D_t and SPI moved in the same direction. In two cases D_p/D_t increased, while SPI did not vary significantly. The mean D_p/D_t for the group increased by 31.8% ($P < 0.005$). In five patients, D_p/D_t of the carotid upstroke was compared with that of the left ventricle; both faithfully reproduced the same directional changes followed by the SPI.

Parameters derived from bloodless carotid pulse tracings, particularly D_p/D_t, may permit clinical evaluation of the inotropic action of cardiac glycosides.

Absence of Baroreflex Bradycardia in Renal Hypertensive Rabbits (P)

Natalie Alexander, Los Angeles, California

The arterial baroreflex mechanism is said to reset in the presence of high arterial pressure so that sinoaortic reflexes function normally. We examined the acute reflex bradycardia response to a brief rise of arterial pressure in conscious rabbits with renal hypertension of 21 days' duration. The decrease in heart rate was measured 30 seconds after a single intravenous injection of angiotensin (0.2 or 0.4 μg/kg). Reflex bradycardia under these conditions was mediated by carotid sinus and aortic nerves, because reflex slowing was eliminated in ten rabbits subjected to sinoaortic denervation.

In 18 preoperative tests of nine normotensive rabbits in which the diastolic pressures (DP) were 53 to 78 mm Hg, cardiac slowing varied from 15 to 95 beats/minute (average 45) in response to an average 30-second pressure increment of 30 mm Hg (25 to 37). Renal hypertension was produced by unilateral nephrectomy and latex encapsulation of the opposite kidney. Thirty-five tests were done at intervals during 21 postoperative days when DP's were 100 to 130 mm Hg. The 30-second pressor responses to angiotensin were usually the same, occasionally higher, than before operation, but reflex bradycardia was diminished or absent in all rabbits; in three tests heart rate decreased 15 beats/minute, in all others it changed 0 to $\pm$ 10 beats/minute. Complete sinoaortic denervation of renal hypertensive animals greatly enhanced the pressor response to angiotensin.

Conclusion: Throughout a 21-day period of renal hypertension, the reflex bradycardia response to an acute increase in arterial pressure was diminished or absent and showed no tendency to reset toward normal. This contrasted with an apparently normal capacity of the arterial baroreflex mechanism to buffer the pressure rise.

Acute and Chronic Therapy of Refractory Congestive Heart Failure with Ethacrynic Acid

Sidney Alexander, Boston, Massachusetts

Ethacrynic acid (EA) has been shown to be an effective diuretic agent in experimental animals and man; however, its great potency and gastrointestinal side effects have largely limited its use to hospitalized patients. Its role in the chronic management of refractory congestive heart failure has not been determined. Twenty-seven patients in severe chronic heart failure, refractory to aggressive diuretic therapy, have been treated with EA, in doses of 25 to 600 mg daily. Four patients judged terminally ill prior to EA therapy did not respond. In three others only minimal effects were obtained. Twenty patients had excellent or good responses defined as complete, or nearly complete, disappearance of edema fluid. Three patients in refractory acute pulmonary edema had striking, immediate responses to intravenous administration of EA.

Fourteen patients have been maintained on EA after discharge for follow-up periods as long as nine months. Gastrointestinal side effects developed in three, which necessitated stopping use of EA. All of these have died. The remaining 11 patients have maintained their substantial improvement. At least nine had been judged terminally ill prior to EA therapy. Three, initially considered too ill for cardiac surgery, are now being reconsidered for valve replacement. Potassium depletion has been readily corrected.

This experience strongly suggests that EA may be safely and effectively employed in the long-term management of the severely ill cardiac patient. In some patients it has proved to be the only effective means of therapy. Its value in the less severely ill patient remains to be determined.

Slowing of the Heart Rate and Potentiation of Myocardial Contractility Utilizing the Standard Radiofrequency (RF) Pacemaker Implant

Constantine E. Anagnostopoulos, New Haven, Connecticut, Lawrence Eisenberg, Alexander Mauro, New York, New York, Wade G. Holcomb, and William W. L. Glenn, New Haven, Connecticut

One of the advantages of the radiofrequency (RF) pacemakers is that with a relatively simple modification of the external equipment, several differing types of stimulation can be produced. A modified RF cardiac pacemaker was used in a series of experiments on dogs with the standard RF implant receiver. By means of portable additional external circuitry, appropriately timed pairs of stimuli or R-wave coupled stimuli were delivered at the usual variable rate and amplitude.

Determinations of electrocardiographic changes, ventricular pressure, ventricular muscle strain and motility, as well as aortic pressure and flow, demonstrated successful slowing and potentiation of the myocardial contractions. The experiments were carried out in dogs with normal sinus rate, sinus tachycardia, pacemaker-induced tachycardia, and acute left ventricular failure. It was shown that cardiac output, if already compromised, increased following paired pulse stimulation. No fibrillation was observed at the usual voltage settings. RF-paired stimulation was applied clinically.

Previous observations made with direct wire conduction to the myocardium on potentiation of contractility and slowing of the heart rate were confirmed using RF transmission of stimuli. The advantages were studied of adapting the paired-stimulus technique, without an additional operation, to the already implanted, standard RF cardiac pacemaker receiver, in the management of the patient with chronic heart block or postoperative tachycardia.

Wireless Radiofrequency (RF) Cardiac Pacemaker Implant (P)

Constantine E. Anagnostopoulos, Wade G. Holcomb, and William W. L. Glenn, New Haven, Connecticut

Electrode wire breakage has been a significant cause of cardiac pacemaker failures. Previous attempts to eliminate the use of implanted wires have utilized either relatively inefficient radiofrequency (RF) transmission of stimuli or unreliable rechargeable batteries powering an epicardiac pacemaker implant. An efficient and reliable means of "wireless pacemaking" of the canine heart utilizing RF transmission of stimuli to an epicardiac implant-receiver with platinum disc electrodes has been developed over the past year.

The 3-cm diameter implant is four to five times more efficient in converting radiofrequency pulses to direct electrical stimuli than the subcutaneous implant currently in use on RF cardiac pacemaker patients; thus pulses exceeding the cardiac stimulation threshold were possible at distances up to 10 cm from the transmitting antenna, which was located outside the body. Excessive stimuli with close proximity of the receiver to the antenna were avoided by stabilizing the peak

efficiency of conversion of radiofrequency pulses to direct stimuli at 4 cm. Effective use of energy was achieved and the currently available RF cardiac transmitter, battery, and antenna assembly were successfully used with the new wireless receiver more than six months after pacemaker implantation.

Multiple determinations of cardiac motility, optimum electrode size, material, and position, as well as thresholds to stimulation, were carried out in animals with and without surgical heart block. Fibrillation was not observed even at maximum current settings and approximation.

These studies indicate that it is possible to use the "wireless-pacemaker" method more efficiently and reliably than previously.

Interpretation of the High-Frequency Components in the Electrocardiogram as Indicating Diffuse Myocardial Disease (P)

Gary J. Anderson, Ann Arbor, Michigan, Bernhard F. Muller, Eloise, Michigan, and Ernest W. Reynolds, Jr., Ann Arbor, Michigan

Patients with diffuse myocardial disease often show reduced voltage with fine notching of the QRS complexes, suggesting information of value in the higher frequency range. Ninety-seven patients with diffuse myocardial disease and 63 normal controls were studied by recording the electrocardiogram and its derivative with a frequency response expanded to 1,000 cycles/second. Leads V_2, V_4, V_6, and proximity leads X, Y, and Z were recorded. Notching and repetitive fine slurring on either limb of R in leads X, V_4, and V_6 were abnormal. Tracings were graded I through IV, according to the extent of changes.

Ten patients with uncomplicated hypercholesterolemia were not significantly different from normal. In coronary disease, 81% (13 of 16) with evidence of myocardial infarction and 56% (10 of 18) with only angina pectoris showed abnormal high-frequency components. Myocardial infarction produced more extensive changes than angina pectoris. Of 26 patients with primary myocardial disease (polyarteritis, Friedreich's ataxia, amyloidosis, scleroderma, Marfan's, etc.), 62% (16 of 26) showed abnormalities, of which 50% (13 of 26) were grade III or IV. Of this group, 12 of 18 with cardiomegaly by X-ray showed marked changes. Positive results were suggested in 59% by careful interpretation of standard ECG's.

It is concluded that extending the frequency response of the ECG improves the ability to recognize cardiomyopathies and suggests that much valid information of this kind is being ignored in conventional tracings.

Adrenergic Mechanisms Following Treatment with Quinidine

Evangelos T. Angelakos, Joan B. Daniels, and Mary King, Boston, Massachusetts

The possibility was examined that the well-known depressant effect of quinidine (Q) on the heart could be due to interference with normal adrenergic mechanisms affecting myocardial contractility. In dogs treated with Q (20 to 30 mg/kg), there was a distinct α-adrenergic blocking effect regarding the blood pressure responses to injected norepinephrine (NE). However, the positive inotropic action of NE was not affected by Q, indicating that Q has no β-adrenergic blocking action that would account for its negative inotropic effect. Q did, however, affect myocardial catecholamine (CA) stores. In the rabbit, 25 mg/kg of Q produced a small (10 to 20%) but significant decrease in CA stores in both atria and ventricles. In addition, histochemical studies using the formaldehyde condensation technique and the recently developed trihydroxyindole method suggest that Q greatly alters the relative concentrations of "bound" and "free" forms of NE present in cardiac adrenergic fibers. The depression of myocardial contractility produced by Q may be related to these alterations in cardiac catecholamine stores.

A New Instrument for Prolonged Mechanical Cardiac Massage (P)

George L. Anstadt, William S. Blakemore, and Arthur E. Baue, Philadelphia, Pennsylvania

Closed-chest or manual cardiac massage, while often effective, produces low cardiac outputs (CO) and arterial pressures, is difficult to maintain for prolonged periods, and may damage the heart and adjacent structures. An instrument has been designed which fits over the ventricles and delivers direct mechanical massage utilizing alternating positive and negative air pressures to produce systole and assist diastolic filling. Cycle length, rate, and pressures can be varied. Negative pressure within the Silastic lining membrane and a cuff at the base hold the instrument in place below the atria.

Hemodynamic studies in dogs with one to six hours of assisted circulation with the heart in fibrillation demonstrated CO of 90 to 100% of control values (900 to 1,800 cc/min), mean arterial pressures of 75 to 90 mm Hg, and low venous pressures. Atrial, ventricular, and pulmonary arterial pressures were elevated, but the animals had no pulmonary edema. Manual massage produced only 30 to 40% of control CO

with higher venous and lower arterial pressures and was maintained with difficulty. In 20 animals, defibrillation was readily accomplished after up to nine hours of support. In survival studies, all of six animals survived after up to six hours of fibrillation, and two animals survived 10 to 17 hours after nine hours of support; one of these died of chest wall hemorrhage. Behavior, electrocardiograms, and appearances were normal until sacrifice after two months. Serum glutamic oxaloacetic transaminase (SGOT) levels are being evaluated. No gross or microscopic myocardial damage was found. Early experience indicates that prolonged circulatory support can be maintained by this technique with better CO and less trauma than with present methods.

Pathogenesis of the Supravalvular Aortic Stenosis Syndrome in Children (P)

A. U. Antia, Richard D. Rowe, Ole E. Ottesen, S. Levin, and R. E. Cooke, Baltimore, Maryland

Eleven white and three colored children (five from two families), aged two to 16 years, with supravalvular aortic stenosis, were studied to determine the extent of (1) vascular lesions, and (2) any disturbance of renal function and calcium metabolism. Skeletal, psychological, and dental evaluations were also performed.

Clinically, the patients fell into three groups: (A) classical "elfin" facies (I.Q. 42 to 109), four patients; (B) abnormal facies but dissimilar to group A (I.Q. 32 to 77), four patients; and (C) normal facies (I.Q. 90 to 118), six patients.

Other observations in groups A and B included hypertension, renal function impairment, abnormal renal biopsies, multiple arterial stenoses, subclavian "steal," and skeletal changes compatible with hypercalcemia. Normal cerebral arteriograms were obtained in four patients. Among group C patients, intimal thickening of the renal artery, multiple arterial stenoses, and hypoplasia of the entire aorta were found.

Evidence for hypercalcemia in groups A and B rests on a raised blood calcium during infancy in one case from group A, renal calcinosis in one child and X-ray bony changes in two children from group B, and a characteristic past history for all these three patients.

All group C patients had infantile feeding difficulties. The apparently normal teeth of one patient showed radiological changes consistent with hypercalcemia. Despite normal I.Q., mental abilities in this group showed the same wide range encountered in patients of the other two groups. These observations raise the possibility that a hypercalcemic etiology might apply to all patients with the syndrome.

Preliminary Study of the Hemodynamic Effects of Alpha- and Beta-Adrenergic Blocking Agents

Agustin Arbulu and Alan P. Thal, Detroit, Michigan

This study was designed to measure the effects of the α- and β-receptor blocking agents on the cardiovascular system before and after suddenly subjecting it to a large fluid load.

Cardiac output, blood pressure, right atrial pressure, and oxygen consumption were measured continuously. The response to 500 ml of commercial dextran injected intra-arterially in 90 seconds before and after adrenergic blockade was measured in 11 dogs ranging in weight from 20 to 30 kg.

Phenoxybenzamine hydrochloride produced a fivefold increase in cardiac output and a fall in total peripheral resistance to one-eighth of control values. Central venous pressure increased only half as much as in controls.

In the six dogs that were given β-blockade with 2.5 mg/kg of nethalide, the response to the fluid load was marked by a much lower pulse rate than control, with only a one-third increase in cardiac output. Central venous pressure rose to four times the control value.

These studies suggest that phenoxybenzamine may be of benefit in clinical situations associated with cardiac failure or vascular overload. Nethalide may be of benefit in tachycardia.

Normal and Abnormal Apexcardiograms

Zdravko Asperger, Bernard L. Segal, Albert J. Kaspar, Moosa Najmi, and Benedict Kingsley, Philadelphia, Pennsylvania

Apexcardiograms from 30 normal healthy adults and 200 patients with acquired heart disease were taken on an EFM simultrace recorder with simultaneous electrocardiogram, indirect carotid pulse, and heart sounds. Simultaneous intracardiac pressures, first and second derivatives of ventricular pressure, sounds, and apexcardiograms were recorded in 25 patients. The timing of opening and closing clicks in prosthetic valves was correlated with the apexcardiogram in 20 patients.

In the normal apexcardiogram, *a* waves reflecting left atrial contraction were recorded in 50%. The large systolic wave began 0.04 second before the initial vibrations of the first heart sound, peaking 0.12 to 0.15 second later (E point). The E point occurred 0.03 to 0.04 second after aortic valve opening determined from simultaneous intracardiac pressures. The positive peak of the first derivative of left ventricular pressure was simultaneous with aortic valve opening. The sharp downstroke of rapid ejection ended

at the lowest point of the apexcardiogram, 0.07 to 0.14 second after the aortic component of the second sound. In 20% of normal curves, the lowest point was synchronous with aortic closure, which preceded the O point, corresponding to the crossover of left atrial and ventricular pressures. The rapid-filling wave was 80° from the horizontal.

The changes on the apexcardiogram in heart disease include: small angle in mitral stenosis, increasing after commissurotomy and valve replacement; sustained systolic plateau in hypertension and aortic stenosis; double-peaked systolic wave in subaortic stenosis; and giant *a* wave in congestive heart disease recorded over the right ventricle (V2 apexcardiogram).

Congestive Heart Failure: A Hereditary Disease Model in the Hamster

Eörs Bajusz, Freddy Homburger, John R. Baker, and C. William Nixon, Cambridge, Massachusetts

An inbred line of Syrian hamsters manifesting a hereditary type of cardiomyopathy that terminates in congestive heart failure has been observed. Both parabiosis and injection of various organ extracts obtained from diseased animals into healthy hamsters failed to transfer the disease. However, genetic studies indicate that this disease, characterized by cardiac and skeletal muscle pathology, is transmitted by an autosomal recessive gene. The morphogenesis of the spontaneous cardiomyopathy was studied in more than 600 hamsters and the progressively developing heart failure was analyzed.

Focal myolysis with primary disappearance of sarcoplasm in the absence of cellular infiltration, the earliest structural abnormality in heart muscle, occurred between the ages of 30 and 70 days. Between 70 and 200 days, the myolytic lesions became more pronounced and increasingly diffuse, and the disintegrated fibers were replaced by connective tissue. Concurrently, frank symptoms of congestive heart failure (e.g., generalized edema, ascites, hydrothorax, liver congestion) developed. Atrial thrombi were occasionally observed in the enlarged hearts of such animals; however, a definite correlation between the generalized cardiac edema and the presence or location of thrombi, the degree of myocardial degeneration and that of skeletal muscle pathology, could not be established. The slow progression of the cardiac condition and its 100% incidence in the homozygous line offers new opportunities for investigative cardiology.

Effects of Ethacrynic Acid on the Kidney

Benjamin H. Barbour, Joseph Hill, and Anneliese M. Barbour, Los Angeles, California

Ethacrynic acid is a new diuretic which has been reported to have a unique physiological effect on water clearance and to have a potency greater than other available diuretics. Sixteen patients were studied to determine the mechanism of the drug's action and its usefulness in clinical edema.

Hydropenia was induced after prolonged sodium restriction (urine Na < 10 mEq/day) and antidiuretic hormone administration in two patients. T^cH_2O was 1 ml/min control, as compared with -1 ml/min at the height of diuresis in the hydropenic, contracted patient. Expansion was induced by a high sodium intake (> 240 mEq/day). In this state, when ethacrynic acid was administered, C H_2O was increased by 6 to 8 ml/min. These effects suggest a proximal tubular action which is contrary to previously reported observations. Sodium diuresis and kaluresis were regularly observed; however, the magnitude of the kaluresis depended upon the state of sodium balance. When patients were sodium-deficient, potassium excretion increased by 100 to 300 μEq/min; when they were sodium-loaded, potassium excretion increased by 20 to 40 μEq/min. The administration of spironolactone appeared to reduce the kaluresis caused by ethacrynic acid, implying its effect was due to delivery of sodium to distal sites. Ethacrynic acid appears to have a proximal site of action and the magnitude of the kaluresis seems dependent upon aldosterone.

Ejected Fraction and Myocardial Contractility

Stuart H. Bartle, J. Francis Dammann, Jr., Charlottesville, Virginia, and Miguel E. Sanmarco, Philadelphia, Pennsylvania

We have attempted to assess myocardial function in patients by using left ventricular (LV) volumes determined by the Dodge-Sandler biplane angiocardiographic method. Eight patients with definite myocardial disease (MD), 32 without MD (many of these had valvular disease), and three patients with variations of the syndrome, idiopathic hypertrophic subaortic stenosis (IHSS), were studied. The ratio of stroke volume to end-diastolic volume, the ejected fraction (EF), was determined as were LV mass, fiber-shortening rates at the circumference (CFSR), mean systolic ejection rate (MSER), and other derived indices of LV contractility.

Results showed a clear-cut differentiation between the groups, with the EF ranging from 0.20 to 0.54 (mean = 0.32) in the adults with MD; 0.55 to 0.73 in the patients without MD; and

0.70 to 0.85 in the patients with IHSS (means $= 0.62 \pm 0.045$ and 0.79 in the last two groups). There was no correlation with EDV, EDP, or MSER; CFSR was considerably lower (2.16 to 2.48 cm/sec) in the patients with MD than in the other two groups (range, 2.46 to 4.38 cm/sec with complete overlap). LV masses correlated with volume and pressure.

The data indicate a remarkably constant EF in the chronically volume-loaded ventricle, even at three times normal volume, as long as there is no definite myocardial disease; the presence of this decreases the CFSR and also the EF. Patients with IHSS managed to increase the EF and therefore may have increased contractility, as postulated by Criley. Measurement of EF and other variables from angiocardiographic volume measurements appears useful in assessing myocardial function.

Silent Ventricular Tachycardia Following Acute Myocardial Infarction

F. A. Bashour and R. E. Edmonson, Dallas, Texas

The cardiac rhythm of 26 consecutive patients with 28 episodes of acute myocardial infarction was monitored with an electrocardiographic tape recorder during the first 24 hours following the onset of chest pain. The same procedure was followed in seven patients with angina pectoris but no infarction. The average age was 54 years (33 to 79 years). Shock was evident in four patients and heart failure in five. Six patients had had previous myocardial infarction. Nineteen patients were asymptomatic during the period of the study. Monitoring began from 1 to 18 hours after the onset of chest pain. Ventricular fibrillation was present in one, complete atrioventricular block in three, and frequent premature ventricular contractions (PVC's) in five patients on admission. In the remaining 17 patients, no irregularity of rhythm was detected clinically.

Multifocal PVC's were recorded on the tape in all patients, and runs of bigeminal rhythm were noted in 11. Ventricular tachycardia occurred in 18 patients (in 20 episodes of myocardial infarction); in 15 of these the rate was 100 or more per minute, and in 5, less than 100. The number of attacks (four beats or more) of ventricular tachycardia in a single patient ranged from 1 to 70. Atrial fibrillation and supraventricular tachycardia occurred in three and five patients, respectively. In the control group, occasional PVC's were recorded.

These observations throw light on the true incidence of clinically significant ventricular tachycardia in patients with acute myocardial infarction, and stress the need for continuous monitoring, since most of the episodes would not otherwise have been observed.

Relationship of the P Wave to Left Atrial Volume and Pressure

William A. Baxley, Richard R. Hawley, and Harold Sandler, Seattle, Washington

The relationship between the P wave of the electrocardiogram and left atrial volume (LAV), left atrial stroke volume (LASV), and left atrial pressure (LAP) was studied in 35 patients. LAV and LASV were determined from biplane angiocardiograms. P-wave duration, amplitude, and direction in the frontal plane, and negative amplitude in lead V_1 were determined. Two patients had no heart disease and the remainder had heart disease of different etiologies, including 20 with mitral valvular disease.

P-wave duration varied from 0.06 to 0.15 second, and LAV from 58 to 344 ml. LAV was related to the P-wave duration with a correlation coefficient (r) of 0.34 ($P < 0.05$). A similar correlation was found between P-wave duration and LASV ($r = 0.42$, $P < 0.02$). No significant correlations were observed for P duration and LAP; for P amplitude and LAV, LASV, and LAP; nor for LAV and the direction of the mean frontal-plane P vector. The amplitude of the negative P deflection in V_1 was not significantly correlated with LAV. No patient had P amplitude in the frontal plane greater than 2.0 mm, regardless of the LAV. Nine patients with a P duration greater than 0.11 second had LAV greater than 110 ml, which exceeds normal LAV. In 20 patients who had enlarged LAV (110 to 344 ml), the P-wave duration was less than 0.11 second. This study demonstrates a low level of correlation between left atrial volume and the P wave of the ECG.

Engineering Analysis of Prosthetic Heart Valves (P)

Jon R. Beeson, Art West, Lafayette, Indiana, and Winton H. Burns, Indianapolis, Indiana

An engineering study of prosthetic valves was undertaken to determine the functional characteristics of various prosthetics. The valves were tested in a pulse duplicator using variable stroke volumes and rates. Pressures and flows were sampled proximal and distal to the valve. The data were recorded on a Beckman/Offner System after being fed through a TR-20 analog computer.

The valves used in the test included: a Starr-Edwards valve, a Pemco valve, a Hufnagel "discoid" valve, a Gott-Daggett type of valve, and three experimental leaflet valves.

The valves were studied at various rates be-

tween 60 and 160 beats per minute; total flow was held constant at 6,000 cc per minute (extremes = ± 3%). All tests were dynamic studies that were conducted at both normal pressures (less than 160 mm) and high pressures (up to 350 mm). The data were analyzed on the following bases: efficiency, opening pressure gradient, maximum gradient, maximum flow gradient, net flow, maximum flow, and back flow.

The results indicate a high rate of efficiency for both the ball valves and leaflet valves at normal pressures and rates. The ball valves have improved efficiencies at abnormally high pressures. At certain rates, the discoid valve was found to fail to close; this failure was as high as 48% (24 of 50) at high pressures. Opening pressures and rate of pressure change were much lower with the leaflet valves. The data suggest that certain advantages exist in leaflet valves over other types of valves, and that the discoid valve may have serious flaws in its design.

Hemodynamic Consequences of Atrial and Ventricular Pacing in Patients with Normal and Abnormal Hearts: Effect of Exercise at a Fixed Atrial and Ventricular Rate

Alberto Benchimol, Joseph G. Ellis, and E. Grey Dimond, La Jolla, California

Fourteen patients, five with normal hearts, six with compensated, nonvalvular heart disease, six with heart failure not on digitalis, all with normal sinus rhythm, were paced at rates of 70 to 200/min with an electrode catheter in the right ventricle and atrium. Two sets of supine exercise at work loads of 306 kg-m/min for four minutes were done by five patients (two normal, three with nonfailing heart disease) while being paced at a fixed rate of 100/min in each chamber.

In normal subjects, responses to right atrial and ventricular pacing were nearly identical. Cardiac index (CI) and tension-time index (TTI) increased by 34% (3.61 to 4.84 L/min/m^2) and 32% (2,414 to 3,176 mm Hg sec/min) as the rate was increased to 110 to 150/min. Stroke index (SI), stroke power (SP), systolic ejection rate (SER), peripheral resistance (PR), and ejection time (ET) decreased by 30% (47 to 33 ml/beat/m^2), 28% (300 to 215 g-m/sec/m^2), 13% (336 to 291 ml/sec/m^2/syst sec), 32% (1,365 to 930 dynes sec/cm^5), and 16% (280 to 236 mm Hg sec/min). CI fell at higher rates.

Exercising normal subjects with fixed atrial and ventricular rates produced identical increases in CI, SI, arterial pressure, dp/dt, ventricular power (VP), TTI, SP, and SER. Patients with heart disease, in failure or not, showed similar responses, but of lesser degree. However, CI and TTI had significantly greater increases during atrial pacing than during ventricular pacing. Exercise at fixed atrial rates produced 56% (2.74 to 4.28 L/min/m^2), 59% (27 to 43 ml/beat/m^2), and 59% (4.77 to 7.57 kg-m/min/m^2) rises in CI, SI, and VP, but increases were significantly less when exercise was done at fixed ventricular rates.

Atrial systole contributed materially to cardiac function in abnormal hearts. During supine exercise at a fixed heart rate, an augmented stroke volume regulated cardiac output.

Influence of Digitalization on the Contribution of Atrial Systole to the Cardiac Dynamics at a Fixed Ventricular Rate (P)

Alberto Benchimol, Marvin S. Liggett, and E. Grey Dimond, La Jolla, California

Eight patients with permanent, fixed-rate ventricular pacemakers implanted because of symptomatic heart block were studied before and 1, 2, 4, 6, 10, 20, 30, 60, 90, and 120 minutes after intravenous administration of 1 mg G-strophanthin. Four patients had coronary arterial disease, four had idiopathic heart block; all had competent hearts. The mean fixed rate was 72/min. The variable P-R interval was measured on the electrocardiogram. Cardiac output was measured by the dye-dilution technique, using cardio-green as indicator. Systemic pressure, ejection time (ET), mechanical systole (S_1S_2), and dp/dt of arterial pressure were measured. Ventricular power (VP), stroke power (SP), stroke index (SI), tension-time index (TTI), peripheral resistance (PR), and isometric contraction (IC) were calculated.

In the control period, a P-R interval of 1 to 300 msec resulted in 25, 18, 30, and 25% increases in systolic arterial pressure (130 to 165 mm Hg), TTI (2,053 to 2,430 mm Hg sec/min), SP (184 to 237 g-m/sec/m^2), ET (234 to 277 msec), and IC (64 to 80 msec), when compared with beats in which the P-R interval fell outside the range of 1 to 300 msec.

Digitalization resulted in 21, 22, 20, and 13% increases in CI (1.98 to 2.40 L/min/m^2), SI (27 to 33 ml/beat/m^2), PR (1,836 to 1,626 dynes sec/cm^5), and VP (3.6 to 4.1 kg-m/min/m^2), maximum response occurring at 10 to 20 minutes. TTI and SP also increased, while ET and IC decreased for any given range of P-R interval. The improvement in ventricular performance following digitalization was not significantly different between beats with a P-R interval of 1 to 300 msec and beats in which the P-R interval fell outside the range of 1 to 300 msec.

Digitalis increases the inotropic properties of the heart, resulting in rises in stroke volume, cardiac output, and mean rate of ventricular ejection, while ejection time and isometric contraction decrease.

Comparative Hemodynamic Effects of Intravenous Isoproterenol and of Ventricular Pacing Matched at the Same Rates in Patients with Complete Heart Block

Lamberto G. Bentivoglio and Harry Goldberg, Philadelphia, Pennsylvania

In six male patients with acquired complete heart block (CHB), hemodynamic studies were performed during intravenous isoproterenol infusion (0.05 μg/kg/min), and during endocardial stimulation by an external pacemaker at the same ventricular rates. Data were also obtained at idioventricular rates.

Group results during idioventricular rhythm, ventricular pacing, and isoproterenol infusion were, respectively: ventricular rate 36, 47, 47/min; atrial rate 83, 78, 107/min; ventilation 5.1, 5.3, 6.2 L/min/m^2; oxygen uptake 117, 123, 135 ml/min/m^2; arteriovenous oxygen difference 7.0, 6.8, 5.1 ml%; cardiac index 1.7, 1.8, 2.7 L/min/m^2; stroke index 47, 40, 58 ml/m^2; pulmonary arterial mean pressure 11.0, 11.5, 13.0 mm Hg; total pulmonary resistance 323, 298, 236 dynes sec cm^{-5}; brachial arterial mean pressure 80, 86, 74 mm Hg; total systemic resistance 2,111, 2,140, 1,257 dynes sec cm^{-5}; left ventricular (LV) systolic ejection period (LVSEP)/beat 0.336, 0.309, 0.281 sec; LVSEP/min 12.3, 14.3, 13.0 sec; LV mean systolic ejection rate 141, 129, 208 ml/ejection sec/m^2; LV stroke work 53, 47, 62 g-m/m^2; LV stroke power 161, 156, 223 g-m/ejection sec/m^2; LV work/min 1.9, 2.2, 2.9 kg-m/m^2.

The hemodynamic superiority of intravenous isoproterenol over ventricular pacing at identical rates depends, most likely, on the synergistic effects of positive inotropism and enhanced venous return characteristic of this drug. The long-term response to isoproterenol, however, is unpredictable and the drug is unable to consistently prevent ventricular standstill and fatal arrhythmias.

Contributions of Private Practice to the Epidemiology of Coronary Artery Disease: Report of a Survey of Physicians

Lawrence Bergner, Lynn P. Garon, Frances R. Gearing, and Morton D. Schweitzer, New York, New York

In an attempt to estimate the magnitude of the problem of coronary artery disease as seen by the physician in private practice, information was obtained from a group of physicians regarding their experience and opinions about coronary artery disease.

In a residential area of New York City with a population of 270,000, physicians in private practice were identified and interviewed. A 70% response rate was obtained. During an average week, the 129 physicians interviewed see at least 630 patients with chronic coronary artery disease, 1,500 patients with hypertension, 54 patients with acute infarctions, as well as a substantial number of patients with other chronic diseases.

In the management of coronary artery disease, only 39% (31 of 79) use anticoagulants during the convalescent phase, a smaller number use them for long-term maintenance, and only a handful as a preventive measure.

Almost all physicians advise restriction of cigarette smoking for patients with coronary artery disease; three of four restrict cigars and pipes as well. Opinions on the probable critical level of serum cholesterol range from 140 to 450 mg%. Dietary advice given to patients is not consistent with physicians' opinions about the relationship between diet and heart disease.

The large number of patients with coronary artery disease treated in physicians' offices and at home serves as a reminder that studies of hospitalized patients do not provide adequate information on the occurrence and variation in the clinical manifestations of this disease. The practices of these community physicians influence the natural history of the disease. The cooperation of these physicians should encourage further epidemiological studies and suggests the possibility of community programs related to etiological factors.

Inhibitors of Platelet Aggregation as a Potential Adjunct in Anticoagulant Therapy (P)

Herbert J. Berman and Nancy E. Niessen, Boston, Massachusetts

Heparin and bishydroxycoumarin are effective inhibitors in vivo of fibrin clot formation, but not of platelet thrombosis. Recently, several substances have been discovered that inhibit platelet aggregation in the test tube. We have studied the effect of one such platelet inhibitor, arginine methyl ester (AME), on platelet thrombosis in vivo by quantitative microelectrode procedures applied to blood vessels in the cheek pouch of 75 hamsters. The measure of susceptibility to platelet thrombosis was taken to be the minimum square-wave electrical stimulus of a millisecond duration that would produce a platelet thrombus in a venule observed at 120 magnifications. Current was measured on an oscilloscope placed across a precision resistor in the circuit.

Intravenous infusion of a 0.015 M AME solution at 0.25 ml/hour produced a 1.6-fold increase in the threshold. Topical application of AME in increasing concentrations progressively elevated the thrombus threshold; for example, 1.2 × at 0.015 M and 2.9 × at 0.10 M. Heparin applied

topically in a concentration of 200 U.S.P. units/ml produced a 1.3-fold increase in the threshold. Heparin (200 units/ml) and AME (0.015 M), when applied topically after mixing, increased the threshold 210%, proving that these compounds have a synergistic effect on the thrombus threshold. They had a similar effect on local bleeding and thrombus formation times.

The experiment has shown that AME, an inhibitor of platelet aggregation in vitro, effectively inhibits platelet thrombosis in vivo. It has a distinct synergistic effect when used in conjunction with heparin in preventing platelet thrombosis.

Factors Affecting Survival in Infants Undergoing Cardiovascular Surgery

William F. Bernhard, Roland U. Navarro, Hiroshi Yagi, and James G. Carr, Boston, Massachusetts

Corrective or palliative cardiovascular surgery was performed in 125 infants under hyperbaric conditions. Eighty-eight cyanotic babies (pulmonary or tricuspid atresia, tetralogy of Fallot, transposition of the great vessels) comprised group I, and 37 acyanotic patients (aortic or pulmonic stenosis, coarctation, ventricular septal defect, atrioventricularis communis, anomalous left coronary artery) formed group II. Metabolic alterations were apparent in 65% (82 of 125 cases), with most profound changes among 90 babies under six months of age.

In group I, precompression studies indicated: arterial pO_2 range, 15 to 40 mm Hg; lactate-pyruvate ratios, 25 to 70 (inversely proportional to pO_2); excess lactate, 1.5 to 4.0 mM/L; pCO_2, 25 to 50 mm Hg; pH 6.80 to 7.25; and an elevated plasma catecholamine concentration (8 to 15 μg/L). Following compression (30 to 44 pounds per square inch), arterial oxygen tension increased (40 to 80 mm Hg), mixed venous pO_2 was unchanged, and occasional hypercarbia developed (pCO_2, 50 to 70). Lactate-pyruvate ratio, excess lactate, and catecholamines generally decreased by conclusion of the operation. Sixty-nine of 88 infants survived (80%).

Metabolic and respiratory acidosis were also detected in 22 of 37 group II patients. Associated congestive failure resulted in reduced pulmonary compliance (0.4 to 1.0 ml/cm H_2O/kg), low pH (7.10 to 7.30), and hypercarbia (pCO_2, 55 to 75 mm Hg). Lactate-pyruvate ratios and excess lactate were not elevated unless hypotension or ventricular fibrillation ensued. Thirty of 37 patients survived. Correction of acidosis in conjunction with a hyperbaric-induced increase in tissue oxygen availability are major adjuvants in infant cardiac surgery.

Telemetric Monitoring of the Electrocardiogram in Acute Myocardial Infarction

Arthur Bernstein, Edwin L. Rothfeld, Victor Parsonnet, and I. Richard Zucker, Newark, New Jersey

A relay telemetric system has been developed for the continuous long-term recording and monitoring of the electrocardiogram in patients with acute myocardial infarction. We feel that this apparatus is superior to other devices because it frees the patient from all mechanical and electrical contrivances that could contribute to his anxiety and discomfort. In essence, the system consists of a transistorized transmitter attached to the patient and a receiver designed to record the data on a dual-channel magnetic tape. The receiver has an arrhythmia detector sensitive to any change in R-R interval or R-wave amplitude.

We have monitored 32 patients with acute myocardial infarction for the first 72 hours after their admission to the hospital. Some disturbance in rate, rhythm, or conduction occurred in 28 cases. Ventricular premature systoles were frequently detected, and paroxysms of ventricular tachycardia were noted in 17 patients; most of the latter were transient, lasting 6 to 20 cycles, and were undetected clinically. However, in two cases there was rapid deterioration into fatal ventricular fibrillation. Atrial arrhythmias and conduction defects were usually seen in diaphragmatic infarction. Three patients with complete heart block were treated temporarily with a transvenous pacemaker until sinus rhythm was spontaneously restored.

Constant electrocardiographic monitoring is essential for the detection and rational treatment of arrhythmias that arise in the course of acute myocardial infarction. In addition, tape recording allows for careful study of those electrical events that herald the onset of serious arrhythmias and the effects of cardioactive drugs on these phenomena.

Prevalence of Sickle Cell Disease in Patients with Rheumatic Heart Disease

Ira J. Bernstein, Rolf M. Gunnar, John R. Tobin, and Raymond J. Pietras, Chicago, Illinois

Conflicting reports in the medical literature state that the prevalence of sickle cell disease is both greater and less than normal in persons with rheumatic heart disease (RHD). In addition, evidence has now been accumulated demonstrating that sickle cell trait, AS, is not a benign condition. Therefore, 106 consecutive Negro patients with RHD were studied to determine the prevalence of these hemoglobinopathies. The group was composed of 70 females and 36 males. An

attack of acute rheumatic fever was documented and/or obtained in the histories of 72 patients. Cardiac catheterization was performed in 45 patients, 14 of whom underwent cardiac surgery. Four patients have subsequently died; autopsies were performed in two. The following cardiac valvular lesions were diagnosed; mitral stenosis, 61; mitral insufficiency, 58; aortic stenosis, 28; aortic insufficiency, 61; tricuspid stenosis, 2; tricuspid insufficiency, 4; and pulmonary insufficiency, 1. Hemoglobin electrophoresis revealed the homozygous sickle state, SS, in three; the sickle cell trait, AS, in 13; and AC hemoglobin in three.

Fifteen per cent (16 of 106) had the sickle defect of the beta chain, indicating a greater-than-normal prevalence compared with several large published series performed in general Negro hospital populations. Of interest was that the subgroup with a hemoglobinopathy had a 1.4-times greater rate of cardiac catheterization than the rest of the patients. Although this series is small, these observations suggest an increased severity of chronic rheumatic valvulitis and an increased predisposition to the acquisition of rheumatic heart disease in patients who have the sickle cell defect.

Simultaneous Bilateral Cerebral Blood Flow and Metabolism with Arteriographic Correlation in Unilateral Brain Infarction

Edmundo Beteta, Peritz Scheinberg, Oscar M. Reinmuth, Sherif S. Shafey, and Sadatomo Shimojyo, Miami, Florida

Simultaneous bilateral determinations of cerebral blood flow and oxygen consumption were made in 12 subjects with predominantly unilateral cerebral vascular disease. Blood flow determinations were made by the original nitrous oxide technique in all subjects, and also by the I^{131}-iodoantipyrine method in seven of the subjects. Each patient was carefully evaluated clinically, and arteriography was performed to visualize the entire extra- and intracranial cerebral circulation for comparison with the blood flow studies.

Cerebral blood flow and oxygen consumption were greatly reduced on the side of the infarction as compared with the intact hemisphere in those instances in which arterial occlusion was complete and collateral circulation inadequate. Where there was adequate circulation to prevent infarction, cerebral oxygen consumption was maintained despite arterial stenosis which greatly reduced homolateral blood flow.

In patients with cerebral infarction whose arteriograms failed to reveal occlusive vascular disease, cerebral blood flow was not greatly reduced on the side of the infarction. Cerebral oxygen consumption was not greatly reduced on the side of small capsular infarctions, despite profound neurological disturbance. Severe occlusive cerebral vascular disease caused a profound reduction in cerebral blood flow and metabolism, but this was not incompatible with survival and even considerable improvement.

Vagal Tuning: A New Concept in the Treatment of Supraventricular Arrhythmias and Heart Failure (P)

Aydin M. Bilgutay and C. Walton Lillehei, Minneapolis, Minnesota

Under normal conditions, the cardioinhibitory center exerts a tonic restraining effect upon the heart rate via the vagi. Evidence indicates that release of this vagal tone is instrumental in triggering supraventricular arrhythmias, atrial fibrillation, etc., as these arrhythmias can be brought under control by increasing the vagal tone either by reflex stimulation (pressure on carotid sinuses) or, chemically, by digitalis or parasympathomimetic drugs. Extreme tachycardia from any cause results in limited ventricular filling, with a fall in cardiac output. In conditions of myocardial exhaustion and congestive heart failure, associated tachycardia reduces cardiac output and efficiency.

To ascertain the effects of restoring vagal tone by selective stimulation of the vagus nerve in conditions under which the heart is beating at a disadvantageous rate and rhythm, we developed external and implantable transistorized "vagal tuners." Controlled slowing of heart rate down to half the starting levels can be achieved readily while preserving the sinus rhythm and maintaining ventricular and systemic pressures. Pulse pressure increases, suggesting increased stroke output. Vagal tuning brings immediate control over ectopic beats, bigeminy, and supraventricular tachycardias induced by electrical stimulation of the atria, by anoxia, or by various anesthetic and sympathomimetic drugs. Vagal tuning in conjunction with the sympathomimetic drugs offers a unique opportunity to overcome low cardiac output by utilizing these drugs for their advantageous vasodilating and inotropic effects, while controlling their chronotropic effects.

Factors in the Regulation of Plasma Angiotensinase in the Rat

Adil E. Birbari and Roger B. Hickler, Boston, Massachusetts

Plasma will inactivate angiotensin through its angiotensinase activity. Factors affecting this activity were studied in rats. The effect of intra-arterial solutions of 0.9% and 5% saline, 25% mannitol, 25% albumin, and 100 μg aldosterone was determined for each stimulus in groups of ten

nephric and ten anephric rats. The effect of ureteral ligation was also determined before and four hours after the procedures described above.

In the nephric group, saline infusions and ureteral obstruction produced a twofold increase in plasma angiotensinase activity over control levels ($P < 0.05$); albumin, mannitol, and aldosterone produced a threefold increase in activity ($P < 0.001$). No relationship was found between change in angiotensinase activity and urinary volume, urinary sodium, or plasma electrolytes.

In sharp contrast, the anephric group failed to respond to the albumin and mannitol, which remained primarily within the vascular space, while the saline infusions again produced a twofold increase ($P < 0.01$), and aldosterone a threefold increase ($P < 0.001$), in plasma angiotensinase activity.

From these studies, the most plausible hypothesis is that two factors are responsible for the observed increase in plasma angiotensinase activity: (1) a rise in extravascular pressure (intrarenal and probably intratubular in the nephric rats, and interstitial in the anephric rats); and (2) a direct aldosterone stimulus (in which the kidneys do not have an obligatory role). This could represent a negative feedback mechanism in the angiotensin-aldosterone system.

Subcutaneous Series Prosthetic Left Ventricle Externally Energized (P)

William C. Birtwell, Fabio Giron, Wendell B. Thrower, Harry S. Soroff,† Ulises Ruiz, and Ralph A. Deterling, Jr., Boston, Massachusetts

A prosthetic left ventricle has been developed which makes use of clinically proved components and requires no internal source of energy. A Teflon vascular graft was anastomosed in 15 animals end-to-side to the aorta at the subclavian level. The graft is brought out of the apex of the thorax in a subcutaneous pedicle which lies parallel with the spinal column, and re-enters the thorax at the level of the fifth interspace. An end-to-side anastomosis of the graft is then made to the descending aorta. The aorta is occluded distal to the proximal anastomosis, thus directing aortic flow distal to the brachiocephalic trunk through the graft. The ventricle is energized externally by a specially developed pneumatic actuator. The graft is compressed during diastole and allowed to expand during systole. The systolic pressure and the left ventricular work were reduced by 20 to 40%. The diastolic pressure was elevated by 30%, thus increasing the perfusion pressure of the coronary arteries.

A ball-check valve was then inserted in the distal portion of the graft in *five* animals. The aortic valve of the animal then functioned as the mitral valve and the left ventricle was atrialized. When the graft was actuated, the pressure work of the left ventricle was reduced by 60 to 70%, and the cardiac output rose by 35%. This preparation makes intermittent operation possible and eliminates ascending infections associated with intrathoracic mechanisms.

Cardiovascular Alpha-Adrenergic Properties of Dopamine (P)

William L. Black and Ellis L. Rolett, Chapel Hill, North Carolina

Previous studies in our laboratory have demonstrated an apparently pure β-adrenergic cardiovascular response to dopamine infusions (1 to 10 μg/kg/min) manifested by: (a) progressive increases in left ventricular (LV) stroke volume (SV), mean systolic ejection rate (SER), ejection fraction (EF), and peak velocity of pressure rise (dp/dt); and (b) decreases in ejection time, end-systolic volume, aortic (Ao) diastolic pressure, and peripheral resistance (PR). To evaluate the adrenergic properties of dopamine further, ten chloralose-anesthetized dogs received dopamine infusions of 5, 8, and 10 μg/kg/min following β-receptor blockade.

Control observations obtained 30 minutes after propranolol (0.4 mg/kg) included cardiac output, EF (0.28, thermodilution), LV and central Ao pressures, and dp/dt. From these data, SV (26 ml), SER (127 ml/sec), circumferential shortening rate (CSR, 9.0 cm/sec), and PR (4,370 dynes $\cdot$ sec $\cdot$ cm^{-5}) were calculated. During peak dopamine infusions, α-receptor blockade was accomplished with phenoxybenzamine (1.5 to 3.0 mg/kg). Dopamine administration following β-receptor blockade produced a progressive decline (expressed as percentage of control) in SV ($77 \pm 4.8\%$), SER ($77 \pm 4.8\%$), CSR ($87 \pm 4.1\%$), and EF ($89 \pm 4.6\%$). PR increased to $156 \pm 18.7\%$. There was a slight decline in heart rate, but no change in LV and Ao pressures or dp/dt. Phenoxybenzamine dramatically returned all observations to control values.

It is concluded that at these dose levels dopamine has significant α-adrenergic properties which are normally masked by its potent β-adrenergic action. In the presence of β-receptor blockade, the net effect is increased PR with consequent decrease in fiber-shortening velocity of the afterloaded left ventricle. Combined α- and β-adrenergic activity suggests that dopamine acts either through norepinephrine release or as a substitute for norepinephrine at both receptor sites.

Changes in Cardiac Performance Following Propranolol in Anesthetized Dogs

William L. Black and Ellis L. Rolett, Chapel Hill, North Carolina

It has been postulated that the myocardial depressant effects of anesthetics are often masked by concomitant augmentation of sympathetic nervous system activity. Elevated plasma catecholamine levels during general anesthesia have been reported. Pronounced changes in canine left ventricular (LV) function during pentobarbital anesthesia have been observed, whereas chloralose anesthesia produced virtually none. Because morphine-chloralose-urethan is a commonly used combination in physiology laboratories, studies of LV performance were conducted before and during β-adrenergic blockade in ten dogs anesthetized with these agents.

LV pressure, peak rate of pressure rise (dp/dt), ejection fraction (EF, thermodilution), and cardiac output (CO) were measured; end-diastolic volume (EDV), mean circumferential shortening rate (CSR), mean systolic ejection rate (SER), and peripheral resistance (PR) were computed. Premedication with morphine sulfate, 3 mg/kg intramuscularly, was followed by 50 to 70 ml intravenously of a chloralose (1.6%) and urethan (16%) mixture. Base line mean values obtained one and a half hours later were: dp/dt, 3,850 mm Hg/sec; EF, 0.36; CO, 3.10 L; CSR, 13.3 cm/sec; SER, 172 ml/sec; and PR, 3,200 dynes · sec · cm^{-5}. Repeat measurements 30 minutes after β-blockade with propranolol, 0.4 mg/kg, revealed significant changes ($P < 0.05$) in nine dogs. These values (units as above) were: dp/dt, 2,496; EF, 0.28; CO, 2.25; CSR, 9.0; SER, 127; and PR, 4,370. Mean LV end-diastolic pressure rose 2 mm Hg. No significant changes in EDV, heart rate, or aortic pressure occurred.

The inhibition of LV performance by propranolol suggests an enhancement of β-adrenergic activity by the anesthetic agents used. Increased catecholamine release may be important in maintaining relatively unchanged cardiac function during anesthesia with these drugs.

Reduction of External Cardiac Work in the Treatment of Cardiogenic Shock (P)

Jack H. Bloch, Charles H. Pierce, and Richard C. Lillehei, Minneapolis, Minnesota

The mortality rate among patients with shock accompanying myocardial infarction remains high (up to 90%). Improvements in treatment of this syndrome have perhaps been hampered by lack of a suitable experimental model. We have hemodynamically characterized cardiogenic shock in closed-chest dogs by embolizing the coronary arteries with microspheres in a dose based on estimated heart weight. Of the animals developing shock, 85% died within 24 hours. The shock syndrome produced is characterized by a low cardiac output and high peripheral resistance. Treatment has centered upon the use of phenoxybenzamine or low-molecular-weight dextran to lower peripheral resistance and reduce external pressure work of the heart, and the administration of levarterenol to phenoxybenzamine-treated dogs to increase cardiac output. We have previously shown that levarterenol alone increases the external work of the heart, lowers cardiac output, and accelerates death. Both phenoxybenzamine and low-molecular-weight dextran (LMWD) lower peripheral resistance, improve cardiac output, maintain adequate organ perfusion at blood pressures of 70 to 80 mm Hg, and increase survival to 75%. In addition, LMWD expands the blood volume. Phenoxybenzamine and levarterenol, in combination, lower peripheral resistance, increase cardiac output above normal, and maintain higher arterial pressures; but survival is similar to that with phenoxybenzamine alone. With this basis, we have treated selected patients suffering shock due to myocardial failure with adrenergic blocking agents and low-molecular-weight dextran, with similar results.

Endothelial Binding of Free Fatty Acid and Vascular Thrombosis (P)

Walter L. Bloom, Atlanta, Georgia

The failure of dextran to prevent venous thrombosis by sodium morrhuate prompted a study of the mechanism of thrombosis by free fatty acid. Titration of thrombosis of the marginal ear vein of a rabbit showed 5 mg of free fatty acid as a 100% (10/10) minimum effective dose. Isolated free fatty acids from rat, rabbit, human liver, and plasma were found to be thrombogenic. Dilution of free fatty acid with citrate or saline did not prevent thrombosis. Comparable dilution with plasma or serum prevented thrombosis. Visible thrombosis often did not occur for periods up to 24 hours.

These results suggested that: (1) the fatty acid effect was not on coagulation; and (2) protein binding of fatty acid occurred and could either cause or prevent thrombosis. To test the latter point, divided nonthrombogenic doses of fatty acid were injected: 0.2 mg produced no thrombosis, 5/5 in 24 hours; 0.2 mg four hours apart produced thrombosis 4/5 in 24 hours.

To test endothelial binding, the dog's femoral vein was flushed of blood, free fatty acid was instilled in the vein and then flushed out, and blood flow returned. Venous thrombosis occurred in 5/5. The contralateral vein identically treated with buffered saline served as the control. Microscopic

studies demonstrated endothelial damage, thrombosis, and venous inflammation following treatment with fatty acid. It has been shown that free fatty acids can bind with the endothelial surface and produce inflammation and thrombosis.

Relationship of Cerebrovascular Reactivity to Degree of Extracranial Vascular Occlusion (P)

Byron M. Bloor, Reza P. Asli, George R. Nugent, and Hisham S. Majzoub, Morgantown, West Virginia

Changes in cerebral blood flow (CBF) and cerebrovascular resistance (CVR) resulting from induced changes in arterial pCO_2 have been studied in 15 patients with varying degrees of occlusive extracranial vascular disease.

Total CBF was measured by the dye-dilution method. End-alveolar CO_2 was continuously monitored and frequently checked with arterial samples. CBF determinations were made after the patients were stabilized at a high and a low pCO_2 level, both before and after endarterectomy. The cerebrovascular reactivity was estimated by plotting the log of the CVR versus the arterial pCO_2 and calculating the slope of the line. A negative slope indicated vascular reactivity; a positive slope indicated absent reactivity.

Decreased cerebrovascular reactivity was found to be related to the extent of vascular disease. In those patients with less than two major arterial inputs involved, a nearly normal reactivity slope (−0.75) was observed preoperatively, and this was only slightly improved postendarterectomy. Conversely, those patients with more severely compromised arterial input demonstrated no reactivity to a change in arterial pCO_2 (average: +0.16), and CBF was dependent on the blood pressure. Postoperatively, the cerebrovascular reactivity was restored to an average slope of −0.64, and in proportion to the success in restoring normal arterial input.

Effect of Exercise on the Extracoronary Collateral Circulation

Colin M. Bloor and Arthur S. Leon, Washington, District of Columbia

Although exercise has been shown to increase the size of the coronary arterial tree, including intercoronary anastomoses, its effect on the extracoronary collateral circulation is unknown. The diameters of the extracoronary collateral arteries in rats have been shown to enlarge under the influence of sex hormones. In the present study, the cross-sectional areas of these extracoronary collateral vessels were determined in male rats of the Walter Reed strain subjected to varying degrees of exercise.

For ten weeks, 17 rats swam in a 30-gallon tank for 30 minutes twice a day (group A), while 16 rats swam for 60 minutes twice a week (group B). After sacrifice of these groups and 20 nonexercised rats (group C) of similar weight, the aortas were cannulated and perfused retrogradely with 10% formalin at a pressure of 100 mm Hg. After fixation, dry ventricular weights were obtained and sections of the extracoronary collateral, carotid, and internal mammary arteries were taken. These sections were projected by a camera lucida to constant magnification and the vessel cross-sectional areas measured with a planimeter.

Cardiac hypertrophy was present to a similar degree in both exercise groups. The areas of the extracoronary collaterals in the A and B groups were 140% and 69%, respectively, larger than those of the C group ($P < 0.001$). The areas of the carotid and internal mammary arteries in the exercise groups were similar to those in the C group, with the exception of the internal mammary arteries in the A group, which had areas 45% greater than the controls ($P < 0.02$).

These observations suggest that exercise to the degree of producing cardiac hypertrophy results in an increase in the size of the extracoronary collateral circulation. The functional significance of this increase remains to be determined.

Effect of Chlorphenisate with Androsterone upon Serum Lipids

Morton D. Bogdonoff, Edward S. Orgain, and Carolyn Cain, Durham, North Carolina

Chlorphenisate combined with androsterone was investigated over a ten-month period to determine its efficacy in lowering serum levels of cholesterol, triglyceride, and phospholipid in a group of 24 patients (10 females and 14 males) who presented significant elevations in serum lipids as follows: cholesterol levels, 255 to 878 mg%; triglyceride levels, 175 to 5,265 mg%; and phospholipid levels, 176 to 930 mg%. The ten-month investigative study was divided into three treatment periods following one month of control observations: (1) placebo—two months; (2) drug —five months; and (3) postdrug placebo—two months.

The mean changes in serum lipids expressed in milligrams per cent for each treatment period were as follows:

	Cholesterol	Triglyceride	Phospholipid
Placebo	−4	−190	−9
Drug	−82	−259	−47
Postdrug placebo	+48	+273	+35

All of the serum changes during administration of the drug are significant at the 0.05 level or

greater. The postdrug increases in cholesterol and phospholipid are also significant, indicating a considerable rebound.

It is concluded that this compound provides effective reduction in serum levels of cholesterol, triglyceride, and phospholipid without incurring distressful side effects. The decrease in lipid levels is quickly reversed when the medication is discontinued.

Effect of Heart Rate on Performance of Starr-Edwards Prosthetic Valves (P)

O. Willis Boicourt, J. David Bristow, Herbert E. Griswold, and Albert Starr, Portland, Oregon

The discrete sounds produced by prosthetic ball valves allow study of physiological events in the cardiac cycle. Sixteen patients were studied with multichannel phonocardiography two weeks to two years after multiple valve replacement.

At heart rates of 60 or below, the mitral closing sound was small and occurred immediately after the Q wave of the electrocardiogram, suggesting that at slow rates the mitral gradient was abolished and the ball had returned toward the closed position before the next systole.

Diastolic filling period (dfp) was estimated by measuring the interval between opening and closing sounds of the mitral or tricuspid valves. In six patients with atrial fibrillation, an estimation of diastolic filling at various heart rates was obtained. When dfp was plotted against the R-R interval, the regression lines were very similar in all six, and slopes ranged from 1.03 to 1.15. The expected close correlation between dfp and heart rate was reflected by correlation coefficients ranging from 0.96 to 0.99. Extrapolation of these lines gave estimates of the critical heart rates at which diastolic filling might be predicted to cease. The validity of these values is supported by measurements in two patients with rapid ventricular rates. The heart rate for predicted absence of diastolic filling varied from 150 to 178 for tricuspid prostheses and from 150 to 189 for mitral prostheses.

The results indicate the importance of maintaining ventricular rate in the physiological range in patients with prosthetic valves and atrial fibrillation, and of prompt treatment of other spontaneous tachycardias.

Determination of the Sequence of Ventricular Depolarization from Isopotential Surface Maps (P)

John P. Boineau, Madison S. Spach, Theo C. Pilkington, Thomas M. Gallie, and Judith B. Gabor, Durham, North Carolina

The complete distribution of body surface potential has been correlated with the process of ventricular excitation in the dog. The instantaneous display of surface voltage has been presented in the form of isopotential maps for every 2.2 msec of excitation. Using an Ampex DAS-100 system, five thoracic electrocardiograms and a reference tracing are simultaneously obtained. A total of 200 points are recorded from a standardized grid drawn on the torso. Cathode followers are used to insure lead isolation, and all data are recorded on magnetic tape at 15 inches per second. The frequency response of the system is flat to 5,000 cycles per second. The data are processed automatically for input to an IBM-7072 computer with the use of an AIL-1401 analog-to-digital converter at a sampling rate of 926 samples per channel per second. The surface maps are constructed from the format of the computer output whereby the voltages for all 200 positions are simultaneously displayed for a specified instant relative to the R peak in the reference tracing.

Complete ventricular excitation studies were performed on the same animals using multipolar myocardial (Scher) electrodes. A global composite of activation is necessary for correlation with the body-surface data.

The results of these investigations demonstrate that there is additional nondipolar information at the body surface. Direct experimental data are provided which indicate that these distributed gradients of potential can be correlated with ventricular depolarization. It is shown that the principal bipole field is produced by radial excitation about an electromotive axis of symmetry. Also, it is demonstrated that secondary fields created at the epicardial and endocardial boundaries are superimposed on the principal field, resulting in increased surface voltage complexity. Proximity augments the detection of these multipoles. By serial inspection of the surface maps, the sequential and distributive characteristics of ventricular depolarization can be determined.

Separation of Erythrocyte Aggregates by Fibrinolytic Activation

Ted P. Bond, John R. Derrick, and M. Mason Guest, Galveston, Texas

Aggregation of erythrocytes into clumps or sludges which block flow in the microcirculation occurs following trauma. Aggregates in dog mesenteric vessels which blocked microcirculatory flow were produced by cooling animals to 15 C, by immersing the posterior half of anesthetized animals in boiling water, by crush injuries, by infusion of thrombin, and by infusion of endotoxin. In each of these experimental states, activation of profibrinolysin (plasminogen) to fibrinolysin (plasmin) by the intravenous administration of streptokinase and a small amount of human plas-

ma brought about a break-up of the erythrocyte aggregates and re-establishment of microcirculatory flow. Cinematographic records were made of these observations at both high speed (3,200 frames/sec) and conventional speeds. The results obtained supply evidence that both fibrinogen and fibrin influence adhesive aggregation of formed elements of the blood.

Computer Analysis of Frank-Lead Electrocardiographic Data Recorded in an Epidemiological Study (P)

E. Raymond Borun, John M. Chapman, and Frank J. Massey, Los Angeles, California

Computer analysis of tape-recorded electrocardiographic records may provide precise, objective, and reproducible measurements of the large mass of ECG data obtained in population studies. The computer program developed by Pipberger and co-workers, which provides both scalar and vector analysis of orthogonal-lead data, appears to be most suitable for this purpose. The Pipberger program was modified and tested on digitized samples of tape-recorded Frank-lead tracings from 900 participants in the Los Angeles Heart Study. Computer measurements of scalar and vector variables were compared with hand measurements of analog tracings transcribed from the same magnetic tape records.

In each lead, the mean difference between computer and hand measurements of the major QRS deflection in 156 complexes from 52 subjects was less than 0.01 mv, and standard deviations for the differences were 0.04 to 0.05 mv. Large errors occurred occasionally in computer measurements of QRS and T variables, and more frequently in measurements of P waves. Abnormal QRS-T patterns observed in scalar and vector-loop tracings were associated with corresponding abnormalities in computer measurements. A group of records from subjects with abnormal standard ECG's was well identified by a multivariate index (Hotelling T^2) computed with constants derived from 315 normal subjects.

The present method for computer analysis of QRS-T variables is suitable for clinical use with appropriate safeguards for detecting technical errors, but the diagnostic quality of information recorded with orthogonal leads requires further study.

Correlation of Frank-Lead Electrocardiographic Data with Age and Body Build in 505 Normal Males

E. Raymond Borun, John M. Chapman, and Frank J. Massey, Los Angeles, California

Corrected orthogonal-lead systems are being used in clinical studies, although there is little evidence that they provide diagnostic information superior to that obtainable from standard or other uncorrected leads with similar methods of data display and analysis. Critical evaluation of the newer lead systems requires information about the range of variation in large samples of healthy individuals as well as in patients with disease.

Amplitudes and durations of scalar variables were measured in Frank-lead electrocardiographic tracings transcribed with a direct writer from records on magnetic tape. Tracings were analyzed from 505 clinically normal adult males who were screened, according to criteria described by Simonson, from 1,328 participants in a population study and 140 college students. Several ECG variables were significantly correlated with age, chest diameter, and relative body weight. Multiple regression analysis indicated that age alone could account for most of the observed correlation. Correlation coefficients (0.2 to 0.5) were not sufficiently large to suggest that regression equations would be clinically useful.

The means and standard deviations for amplitudes of Rx in 144 subjects 20 to 39 years of age, 291 subjects 40 to 59 years, and 70 subjects aged 60 to 79 years were 1.03 ± 0.33, 0.86 ± 0.32, and 0.84 ± 0.32 mv, respectively. In these same groups, the amplitudes for Ry were 0.89 ± 0.37, 0.70 ± 0.32, and 0.50 ± 0.30; for Sz, 0.85 ± 0.32, 0.67 ± 0.25, and 0.55 ± 0.26; and for Tx, 0.29 ± 0.15, 0.19 ± 0.10, and 0.16 ± 0.10 mv. The results indicate that the normal range for Frank-lead ECG data should be stratified by age.

Intracardiac Venoarterial Shunting in Pulmonary Emphysema

Barbara A. Bostock, Edward W. Westura, and Kenneth M. Moser, Washington, District of Columbia

Transient right-to-left shunts have been demonstrated following the Valsalva maneuver in patients with atrial septal defects and altered right ventricular compliance. The same phenomenon has been described in some patients with chronic pulmonary disease, apparently via a patent foramen ovale. Since a potentially patent foramen ovale has been reported in 20% to 60% of the population, such a mechanism might frequently contribute to hypoxemia in patients with chronic lung disease.

This hypothesis was tested in 13 patients with spirometric evidence of moderate to advanced pulmonary emphysema. Right-heart catheterization was performed. Measurements of pulmonary arterial, right atrial and ventricular pressures, arterial blood gas analyses, and indicator-dilution curves were carried out at rest, following the Valsalva maneuver, during exercise, and during 5%

carbon dioxide breathing. Lung radioscans were subsequently carried out.

Mild to severe pulmonary hypertension was present in 10/13 patients at rest. The degree of hypertension did not correlate with the degree of hypoxemia (13/13) or hypercapnia (6/13). No right-to-left intracardiac shunt was demonstrated in any subject at rest or during any of the subsequent study periods. Lung scans disclosed scattered zones of decreased activity in most patients. These observations suggest that despite alterations of right ventricular compliance, a right-to-left shunt via the foramen ovale rarely contributes to hypoxemia in patients with pulmonary emphysema.

Antithrombotic Effect of Malayan Pit Viper Venom on Experimental Thrombosis

Robert E. Botti, James L. Marsten, Chan Kok-Ewe, and Jay L. Ankeney, Cleveland, Ohio

Individuals who are bitten by the Malayan pit viper may develop marked hypofibrinogenemia of prolonged duration. The incoagulable state is surprisingly free of hemorrhage and mortality. In animals, the injection of this viper venom results in a similar hypocoagulable state due primarily to slow intravascular fibrin formation.

A thrombogenic situation was established by placing a single bar of umbilical tape across the lumen of the inferior vena cava. Every dog in a control group of 14 developed on the tape a red thrombus, which could be demonstrated within 24 hours postoperatively. By the seventh postoperative day, four of five dogs at autopsy had complete obstruction of the vena cava by large thrombi. Significant hemorrhage was not noted.

Eighteen animals were given viper venom intravenously almost immediately postoperatively and were then sacrificed one to ten days later. In 16 of these animals, there were no red thrombi, only small fibrin accretions on the tape. The other two dogs developed thrombi; in one of them the thrombi were probably due to an associated pericaval abscess. Three of ten animals had retroperitoneal or intraperitoneal hemorrhage when 15 μg/kg of venom was administered, but bleeding was not noted when 5 μg/kg was used.

Two additional dogs were given 15 μg/kg of venom 24 and 48 hours postoperatively. No thrombi were seen seven days later, suggesting that fibrinolysis, as well as hypofibrinogenemia, may explain the in vivo antithrombotic effect of Malayan pit viper venom. These experiments demonstrate that a benign induced hypocoagulable state prevents venous thrombosis in this unique experimental model.

Identification of Inotropic and Chronotropic Cardiac Effects in Reactive Hyperemia Induced by Tourniquet Ischemia

James T. Botticelli‡ and Ramon L. Lange, Milwaukee, Wisconsin

Arterial tourniquet application to the thighs produces a modest reduction in cardiac output followed by a brisk increase on release as reactive hyperemia ensues. Varying systemic vascular resistance (SVR) may be responsible, but humoral substances from the ischemic limbs may alter cardiac function. This possibility was investigated by repeated examination of the hemodynamic effects of tourniquet application and release for 20 minutes, and also by brief release for one to five minutes and reapplication, thereby isolating the ischemic area. Right-heart and aortic catheterization allowed continuous recording of heart rate (HR), venous (VP), arterial (AP), and pulmonary arterial wedge (PAW) pressures, along with cardiac output (CO) and central blood volume (CBV) by indicator-dilution, stroke volume (SV), and stroke work (SW).

Ten normal subjects showed a postrelease rise in CO (25%). HR decreased 15%, resulting in a significant rise in SV and SW (30%), even though SVR returned to control levels in five minutes. Blockade with tetraethylammonium chloride (six subjects) was followed by more striking changes that persisted for 20 minutes in HR (−30%), SV (+40%), and SW (+60%), since SVR again quickly returned to control values. Reapplication after brief release shortened the duration of increased SV and SW. Hemodynamic parameters returned to prerelease levels by 15 minutes in all subjects. There was only slight random variation in VP, PAW, and CBV.

These observations are interpreted as evidence for prolonged and significant positive inotropic and negative chronotropic cardiac effects in posttourniquet reactive hyperemia. The response resembles that reported with bradykinin administration. By extrapolation, evidence was found that muscular activity may produce significant direct cardiac effects, as well as alter vascular resistance.

Myocardial Glycolysis in the Ischemic State

Norman Brachfeld and James Scheuer, New York, New York

The left coronary artery of the dog was perfused from a reservoir of normoglycemic oxygenated blood at a physiological pH. A hemodynamic steady state was established (mean coronary flow [MCF] = 82 ml/min). Samples of coronary arterial and venous blood (CS) were analyzed for oxygen, glucose, pH, lactate, and pyruvate. After a control period, perfusion was reduced to

an ischemic steady state (MCF = 30 ml/min) evidenced by decreased qO_2 (control [C] = 10.4; ischemia [I] = 5.8 ml/100 g/min), atrial hypertension (C = 6.9; I = 25.0 mm Hg), and significant concentrations of CS "excess" lactate ($\Delta\%$ = +116%; $P < 0.001$), despite fixed concentrations of arterial lactate and pyruvate. Each dog served as its own control. When MCF was reduced, oxygen extraction became maximal; oxygen consumption and pressure time per minute fell. Changes were disproportionate, and calculated myocardial efficiency was increased during ischemia. The coefficient of glucose extraction (A-V/A × 100) rose 404% ($P < 0.001$). Since increased extraction was proportionately greater than reduction in flow, absolute glucose consumption increased 92%.

Increased dependence on glycolytic pathways stimulated the accelerated glucose uptake and utilization. In the ischemic myocardium, compensatory stimulation of glycolysis occurs and anaerobic mechanisms acquire greater significance as an energy source. This effect may account for the apparent increase in calculated efficiency. The data agree with reports of increased glucose uptake by the isolated perfused rat heart and of quantitative conversion of glucose to lactate by anoxic preparations in vitro.

Treatment of Circulatory Shock with a Betamimetic Agent

Edward C. Bradley and Max H. Weil, Los Angeles, California

The administration of the α-adrenergic inhibitor, phentolamine, and an adrenergic drug with primary betamimetic activity, isoproterenol, consistently increased venous return and decreased arterial resistance in dogs. In patients during shock, phentolamine also provoked a significant increase in cardiac output and a decrease in arterial resistance, circulation time, and venous return. In the present study, isoproterenol was evaluated.

Among six patients studied, shock was related to bacterial infection in three and to fluid loss unresponsive to restoration of volume in three. Isoproterenol was infused at an average rate of 4.9 μg/min for an average duration of 20 minutes. In each of eight trials, cardiac output (measured by the indicator-dilution technique with central injection of indocyanine-green dye) increased. Cardiac index increased from an average of 1.6 to 3.2 L/min/m^2 ($t = 3.49$; $P < 0.02$). Unlike in normotensive subjects, in whom arterial pressure is decreased by isoproterenol, arterial blood pressure was increased by an average of 33 mm Hg. Heart rate was increased from 72 to 106 beats/minute ($t = 3.63$; $P < 0.02$) and, simultaneously, stroke volume was elevated from 31 to 49 ml ($t = 3.86$; $P < 0.02$), demonstrating the significant chronotropic and inotropic effects of isoproterenol. Improvement in systemic blood flow was manifested by a reduction in mean circulation time, an increase in peripheral temperature, and an increase in urinary flow.

Betamimetic actions of isoproterenol similar to alphalytic actions of phentolamine provoked these beneficial hemodynamic responses. We confirm MacLean's observation that the betamimetic agent, even more potent than phentolamine, has special promise for improving effective blood flow for the treatment of selected cases of circulatory shock.

Hemodynamic Observations in Acute Myocardial Infarction, Employing Right-Heart Catheterization (P)

Russel W. Brancato, Leonard Weinstein, Danelo R. Canete, Carlo A. Pallini, and Nicholas A. Antonius; Newark, New Jersey

This study was undertaken to develop a program for the intensive care of patients with fresh myocardial infarctions. Continuous observation of hemodynamic as well as electrocardiographic data appeared to offer a sound approach to understanding and treating the acute consequences of this disease.

All procedures were carried out at the bedside. Arterial and central venous pressures were obtained through indwelling catheter needles, which were inserted percutaneously into a femoral artery and the left subclavian vein, respectively. Right-heart catheterization was performed percutaneously, with a small-bore polyethylene catheter, from a femoral vein, to gain access to the pulmonary artery.

Superior vena caval, pulmonary artery, and femoral artery pressures and a single electrocardiographic lead were monitored for the first 48 hours of hospitalization. Cardiac output was determined periodically by indicator-dilution techniques, with pulmonary artery injection and femoral artery sampling; stroke volume, central blood volume, and systemic vascular resistance were thus calculated. Measurements of extracellular blood volume, arteriovenous oxygen differences, and arterial pH and pCO_2 were also done, and several standard 12-lead electrocardiograms were obtained.

From the ten patients followed to date, several significant observations emerge. The procedures are both safe and simple. Coexistence of reduced cardiac output and clinical shock is gravely prognostic, whereas hypotension associated with normal cardiac output has a good prognosis. Rising pulmonary artery pressures suggestive of left-heart failure may be normalized by prompt digitalization. Right-heart failure, accompanied by a low cardiac output, may occur in the face of normal pulmonary artery pressures.

Effects of Mitral Valve Replacement on the Pulmonary Vascular Dynamics of Patients with Pulmonary Hypertension

Eugene Braunwald, Nina S. Braunwald, John Ross, Jr., and Andrew G. Morrow, Bethesda, Maryland

An understanding of the extent to which secondary obstructive pulmonary vascular changes can be reversed by surgical correction of the valvular lesion is of importance when operation is contemplated in patients with mitral valvular disease and marked pulmonary hypertension. The interpretation of earlier hemodynamic studies performed after mitral commissurotomy was often difficult because this procedure frequently resulted in incomplete relief of obstruction. The introduction of prosthetic mitral valves has allowed more definitive determination of the extent of reversibility of abnormalities of pulmonary vascular dynamics in patients with mitral valvular disease.

Pulmonary vascular dynamics were evaluated both pre- and postoperatively in 31 patients with mitral valvular disease in whom the valve was replaced with a Starr-Edwards prosthesis and whose preoperative pulmonary arterial systolic pressures exceeded 50 mm Hg. Fourteen patients had predominant stenosis and 17 had predominant regurgitation. The pulmonary arterial systolic pressures declined from an average preoperative level of 75 mm Hg to 39 mm Hg, while the average gradient across the pulmonary vascular bed decreased from 23 mm Hg to 15 mm Hg. The average resting cardiac output increased from 2.04 to 2.99 L/min/m^2, and the average calculated pulmonary vascular resistance declined from 679 dynes-sec-cm^{-5} preoperatively to 249 dynes-sec-cm^{-5} postoperatively.

No consistent differences were apparent between the responses of patients with predominant stenosis and those with predominant regurgitation. Thus, serious pulmonary vascular changes are not irreversible and should not serve as a contraindication to operation, since valve replacement generally results in striking reductions in pulmonary vascular pressure and resistance in patients with mitral valvular disease and pulmonary hypertension.

Clinical and Hemodynamic Studies after Tricuspid, Mitral, and Aortic Valve Replacement

J. David Bristow, Frank E. Kloster, Albert Starr, Colin W. McCord, and Herbert E. Griswold, Portland, Oregon

Four patients, aged 29 to 38 years, have been observed from 8 to 27 months after triple valve replacement with Starr-Edwards prostheses. Preoperatively, all had gross cardiomegaly and heart failure from trivalvular rheumatic heart disease. Mean right atrial pressures (MRAP) were from 12 to 22 mm Hg in three and normal in one. Right ventricular end-diastolic pressure (RVEDP) was elevated in three patients. Mean left atrial pressure (MLAP) varied from 20 to 27 mm Hg. Cardiac indices were from 1.62 to 1.90 L/min/m^2.

Postoperatively, symptoms are improved, with absence of heart failure and improved exercise tolerance the most striking observations. Some cardiomegaly persists in all patients. One patient had a cerebral embolus and has residual hemiparesis. At postoperative catheterization, two patients had normal intracardiac pressures; cardiac index had increased in both (1.89 to 3.00, and 1.86 to 2.34), and tricuspid valve areas were 2.2 and 1.8 cm^2. The remaining two patients had persistent elevations of MRAP (10 and 12 mm Hg), although one had higher levels preoperatively; RVEDP was elevated in both; cardiac index changes were from 1.90 to 2.78 and 1.66 to 1.83, and tricuspid valve areas were 3.0 and 1.6 cm^2.

Mean diastolic pressure gradients across the tricuspid prosthesis were from 3.0 to 5.5 mm Hg. However, abnormal MRAP was associated with abnormal RVEDP and atrial fibrillation, whereas normal MRAP was associated with normal RVEDP and sinus rhythm. Thus, it is suggested that RVEDP and cardiac rhythm are important determinants of MRAP in patients with tricuspid prostheses.

Red Cell Survival in Patients with Mitral Valvular Disease and Mitral Valve Replacement (P)

Michael T. H. Brodeur, Robert D. Koler, Albert Starr, and Herbert E. Griswold, Portland, Oregon

Radioactive chromium-51 red blood cell (RBC) half-life survival was determined in 14 patients with mitral valvular disease, 7 with mitral Starr-Edwards ball-valve prostheses, 8 with aortic and mitral valve prostheses, and in 20 normal subjects. In addition, hemodynamic studies and routine hematological and antiglobulin tests were performed.

No one with mitral valvular disease was anemic, although four patients with severe mitral disease had moderately shortened red cell survivals (16 to 21 days; normal, 24 to 32 days). Those with mitral prostheses had normal survivals, except for one patient who had associated aortic valvular disease.

In patients with aortic and mitral prostheses, mean RBC survival was shortened to 20 days (range, 16 to 25 days). Previous studies showed subjects with a single aortic prosthesis to have a mean RBC survival of 20 days (range, 14 to 26 days). The addition of a normally functioning

mitral prosthesis did not further shorten red cell survival. However, one patient did develop hemolytic anemia with urinary excretion of hemosiderin and a RBC survival of 13.5 days; the aortic prosthesis was normal, but the mitral prosthesis was malfunctioning.

As in aortic disease, severe mitral disease may cause sufficient intracardiac turbulence to shorten red cell survival. The normally functioning mitral valve prosthesis does not shorten red cell survival. The evidence suggests that a malfunctioning mitral prosthesis in the presence of a normal aortic prosthesis may cause hemolytic anemia.

Vascular Tone in Ductus Arteriosus

Baruch Bromberger-Barnea, Richard D. Rowe, and Imrich Bor, Baltimore, Maryland

The ductus arteriosus of newborn piglets and puppies (under 12 hours) was perfused with blood from a constant-flow pump connected to the aorta under conditions in which the only outflow from the aorta was the ductus itself and the pulmonary arterial pressure could be controlled at any desired level. We studied the relationship between pulmonary arterial pressure and aortic pressure at constant ductal blood flow. The initial level of flow was set at a value that would produce an aortic pressure of approximately 80 mm Hg when the pulmonary arterial pressure was zero.

In eight of ten preparations studied, the pulmonary arterial pressure had to be raised above a critical level before any change in aortic pressure occurred (mean critical level: 50 mm Hg). Above the critical level, increases in pulmonary arterial pressure always caused increases in aortic pressure; below the critical level, aortic pressure remained constant in spite of changes in pulmonary arterial pressure. When the oxygen tension of the perfusing blood was lowered, the critical level fell. When saturated potassium chloride was perfused, the critical level fell to zero.

These observations are compatible with a "waterfall" effect from ductal smooth muscle tone, and the magnitude of the critical level is probably proportional to the degree of tone. The presence of such a critical level means that information obtained from measuring ductal resistance (aortic–pulmonary arterial pressure/flow) can yield misleading and even erroneous information concerning changes in ductal tone.

Serum Triglycerides in Health and in Ischemic Heart Disease (P)

David F. Brown, Sandra H. Kinch, and Joseph T. Doyle, Albany, New York

Serum triglyceride and cholesterol levels were measured in 1,851 middle-aged men who had been examined annually for the preceding eight years and who were subsequently examined annually for the next four years. At the time of the initial triglyceride determinations, 140 men had ischemic heart disease (IHD). An elevated triglyceride or cholesterol level was associated with an increased prevalence of IHD. As both lipids are always present in serum and frequently were simultaneously elevated, it was difficult to ascertain an independent relationship of either lipid to the prevalence of IHD. It was found, however, that in 241 subjects with cholesterol levels greater than 275 mg%, the triglyceride level had no effect on the prevalence rate. Marked hyperglyceridemia with a normal cholesterol level was an uncommon combination, but in the relatively few subjects with this lipid defect, the prevalence of IHD was not impressively high.

Fifty-six subjects developed IHD during a four-year period after a triglyceride level was measured. Although the disease occurred more frequently in association with increasing levels of either cholesterol or triglyceride, the small number of cases made it impossible to ascertain that triglyceride elevation played an independent role with respect to incidence.

It is concluded that in middle-aged men, a triglyceride determination has no advantage over a cholesterol determination in terms of distinguishing subjects with and without IHD, and that in certain subjects, IHD is highly prevalent in the presence of normal triglyceride levels.

Serological Studies on the Viral Etiology of Congenital Heart Disease (P)

Gordon C. Brown, Ann Arbor, Michigan

A study of the incidence of certain viral infections during pregnancy and their relationship to congenital anomalies is in its sixth year. Paired specimens of serum collected early in pregnancy and again at delivery, or single specimens collected at delivery, were tested for Coxsackie, Echo, influenza, and adenovirus antibodies, and the results with sera from mothers of abnormal infants were compared with serology from one or two matched control mothers of normal children.

The incidence of anomalies was 3% (215 of 6,200) and the most frequent type was congenital heart disease (CHD). Forty of the 215 defective infants (19%) showed this condition, but paired mothers' sera were available for only 26. Matched controls for this group numbered 35. These two groups showed no difference in Echo, influenza, or adenovirus infections. However, evidence of 32 different Coxsackie infections during pregnancy was found in the 26 mothers of infants with CHD, as compared with only 23 infections in the 35 controls. At least one Coxsackie infection occurred in

19 of the 26 and in 17 of the 35. These data showed $P = 0.09$ to 0.11 when subjected to an X^2 test of significance. Coxsackie B4 infection occurred nine times in mothers of anomalous children and only four times in control women ($P = 0.06$ to 0.07); the ratio of Coxsackie B1 infections was 6:2 ($P = 0.05$). Although to date the numbers are small, these results are highly suggestive of Coxsackie virus teratogenicity of congenital heart disease and provide the rationale for continued investigation.

Quantitation of S-T Segment Response to Exercise

Robert A. Bruce, John A. Mazzarella, John W. Jordan, Jr., and Elmer Green, Seattle, Washington

One hundred–beat samples of a bipolar precordial-lead electrocardiogram recorded on magnetic tape were summated on a Computer of Average Transients for each period or work load of a multistage maximal exercise test to define the S-T segment responses quantitatively with a tenfold reduction in variation due to high levels of ventilation and artifacts from bodily movements. Dual-track recording was utilized to permit sampling of P-Q segment prior to QRS and T complexes for the same beats. Optimal loci for definition of most stable 0.01-second intervals of P-Q and S-T segments were determined on 18 normal men; standard deviations, even at maximal heart rates, were less than 1% of mean voltages.

Of 57 clinically normal asymptomatic middle-aged men, nine exhibited obvious and nine showed borderline S-T segment depressions in the post-exercise ECG's, while 39 showed normal responses by usual clinical interpretation of tracings. Quantitation of S-T at 0.04 and 0.06 second after nadir of S, and relative to P-Q 0.03 through 0.04 second prior to Q, showed progressive depression with increasing work loads in all, and significantly greater changes, with prolonged recovery, in borderline and abnormal subgroups compared with "normals." QS conduction time shortened ($P < 0.01$) only in the "normals."

Objective, quantitative evaluation of S-T segment responses are feasible for physiological studies of ischemic responses or for epidemiological surveys for identification of individuals with increased risk of subsequent coronary heart disease.

Alpha-Cholesterol Percentage in Coronary Patients and Healthy Controls of Both Sexes

Daniel Brunner, Shmuel Altman, Kurt Loebl, and Sara Schwartz, Jaffa, Israel

Among 305 middle-aged male patients in Israel suffering from ischemic heart disease, 44% had serum cholesterol values higher than 251 mg%, 22% had values between 221 and 250 mg%, 13% between 201 and 220, and 17% had values less than 200 mg%. Among 83 female patients, 16% had serum cholesterol values less than 220 mg%.

Alpha-cholesterol percentage, expressed as a relative value and indicating the percentage of the total cholesterol in the α-lipoprotein fraction, was markedly decreased, irrespective of the level of total cholesterol. Eighty-two per cent of all male patients and 78% of all female patients had an α-cholesterol percentage less than 20%. Among the subgroup of patients (89 men) with total cholesterol levels *less* than 220 mg%, 72% had α-cholesterol under 20%; the corresponding figure for healthy controls was 23%. For women, the corresponding figures were 63% and 6%.

When coronary patients were compared with healthy controls matched in sex and serum cholesterol levels, it was found that α-cholesterol percentage for every cholesterol value (from 160 mg% to 280 mg%) was statistically significantly higher in healthy women than in healthy men, and in healthy men than in male coronary patients. The α-cholesterol percentage of female coronary patients was in the same low range as that found in male patients with identical serum cholesterol values.

It is suggested that α-cholesterol percentage is a valuable parameter indicating atherogenic activity, especially in patients without increased total serum cholesterol. It seems that the first step in the development of an atherogenic lipoprotein pattern is a redistribution of the cholesterol between the α- and β-lipoproteins.

Over Two Years' Experience with Subtotal Ileal Bypass in the Treatment of Patients with Hypercholesterolemia and Atherosclerosis (P)

Henry Buchwald and Richard L. Varco, Minneapolis, Minnesota

Since May of 1963, we have performed subtotal ileal bypass specifically as a means of decreasing the body cholesterol pool. Fourteen patients have had the procedure to date; six will have been followed for over two years. The procedure has markedly lowered cholesterol levels in all of our patients; over one-half have had serum cholesterol values reduced to below 200 mg%. It is now possible to also present preliminary data about the effect of this cholesterol reduction on the atherosclerotic process. At present all of our operated patients are alive, with the exception of one who died on the fourth postoperative day of an acute myocardial infarct. This particular patient had had a previous infarction, as have others in this high-coronary-risk group. Nearly all of the patients report a lessening of angina symptomatol-

ogy and increased work capacity. One of two patients with large-tendon xanthomata has shown visible regression. A conversion of a positive preoperative double Master's electrocardiogram to a negative one has been observed. Comparison analyses of preoperative selective arteriograms and coronary angiograms and repeat studies in the same patients one and one-half years or longer after surgery seem to show evidence of no further progress, and possible reduction, of plaque lesions. These preliminary clinical findings are in good agreement with our experimental results in the rabbit, where ileal bypass has prevented dietary atherosclerosis, arrested arterial disease, and reversed organ deposits, despite continuation of a severely atherogenic diet.

Pulmonary Blood Volume in Shock Following Experimental Myocardial Infarction

Jack Budow and Irving G. Kroop, Brooklyn, New York

In the course of a study to determine the effect of prosthetic-graft replacement of an acute infarct in dogs, measurements of pulmonary blood volume were made before and after acute myocardial infarction. The left anterior descending coronary artery was ligated near the apex. Myocardial infarction with shock occurred in seven dogs. Pulmonary blood volume and cardiac output were measured by the indicator-dilution technique. All measurements were made before and immediately after the onset of hypotension. At the onset of shock, there was a reduction in pulmonary blood volume, cardiac output, and total peripheral resistance. Pulmonary blood volume declined by an average of 29% (86 to 61 ml), cardiac output declined 25% (1.2 to 0.9 L/min), and total peripheral resistance fell 33% (8,479 to 5,671 dynes/sec/cm^{-5}). There was no associated rise in right atrial or left ventricular end-diastolic pressure. The heart rate was not significantly altered.

The observation of a decreased pulmonary blood volume and an unchanging left ventricular end-diastolic pressure may indicate that reduced left ventricular contractility and heart failure are relatively unimportant at the onset of cardiogenic shock. However, the observation of a reduced total peripheral resistance suggests a reflex decrease in peripheral vascular tone to be the primary factor.

Experimental Viral Valvulitis (P)

George E. Burch, Nicholas P. DePasquale, Alfred R. Hale, William J. Mogabgab, and Shih C. Sun, New Orleans, Louisiana

That viruses may produce valvulitis has been suggested from time to time. At present, few, if any, cardiologists consider chronic valvular disease to be viral in etiology. Nevertheless, in a significant number of patients with diseased aortic and/or mitral valves, no history of rheumatic fever or bacterial endocarditis is obtained. The present study was performed to determine if valvular lesions could be produced in mice with Coxsackie group B virus. Accordingly, over 200 mice (HAM/ICR strain) were inoculated intraperitoneally with Coxsackie group B_4 virus. The mice were killed at various intervals ranging from 12 hours to 76 days after inoculation. The hearts, including the valves, were studied by light and electron microscopy. In about two-thirds of the mice, mitral and/or aortic valvular lesions were found. In the early lesions, the valves were edematous and infiltrated with round cells. As the lesions progressed, fibroblastic proliferation followed by fibrosis became evident. Verrucae were present in some of the older lesions. It is evident, therefore, that inoculation of mice with Coxsackie group B_4 virus frequently results in valvulitis. These studies indicate the need for more extensive investigations of the role of viruses in the production of valvular lesions.

Theoretical Model and Experimental Study of the T Wave (P)

Mary Jo Burgess, Kenichi Harumi, and J. A. Abildskov, Syracuse, New York

The T wave is related to the action potential downstroke as the QRS is related to the upstroke. An instantaneous QRS vector (V_n) may be expressed as the product of the potential difference of the action potential upstroke (E) and the length of the line (L_n) which closes the activation front ($V_n = E \times L_n$). Since recovery proceeds slowly, determination of an instantaneous T vector (T_n) must take account of potential differences (e_n) during individual time units of adjacent action potentials.

$$T_n = L_1 \times e_n + L_2 \times e_{(n-1)} + \ldots . L_m \times e_{(n-m+1)},$$

where $$E = \sum_{n=1}^{m} e_n.$$

A computer program was developed for analysis of the action potential–T relation. A representative action potential was divided into 50 to 60 segments and assigned to each of several myocardial areas. The onset of each was made to correspond to the normal activation order, and duration was chosen to approximate available information concerning refractory period. The sum of potential changes during each time unit of several coexisting action potentials was determined. The product of these potentials and L_n was represented as the magnitude of vectors and given directions opposite

those of instantaneous QRS vectors. T waves were plotted and were similar to those recorded experimentally.

Localized myocardial cooling and warming were produced experimentally and functional refractory periods measured. Comparable changes in action potential duration were introduced in the model and, qualitatively, the derived T waves approximated those recorded experimentally. This analysis provides a model in which the T wave is explained in terms of the cellular action potential and ventricular excitation sequence.

Implantable Artificial Heart

Winton H. Burns, Indianapolis, Indiana, R. J. Loubier, and R. G. Bergstedt, Fort Wayne, Indiana

An electrohydraulic implantable artificial heart has been developed for total cardiac replacement. The heart consists of a ventricular unit and an electrohydraulic unit which are interconnected by flexible hydraulic lines. The ventricular package is about four-fifths the size of the normal heart. It is the actual blood pump and contains collapsible ventricles in a semirigid housing. One-piece molded leaflet inflow and outflow valves are used in the ventricles, which are connected to atrial remnants, the pulmonary artery, and the aorta.

The abdominal package is 4½ by 4½ by 1½ inches, and contains a high-output miniature mixed-flow pump, a bistable-fluid logic system, a hydraulic-fluid reservoir, and a venous-return monitor which is used to regulate cardiac output.

Pumping action is achieved by circulating hydraulic fluid alternately between the right and left ventricular housings, thus providing atraumatic blood handling. Rate is self-regulated by a ventricular signal which modulates the bistable-fluid amplifier. Cardiac output is servo-controlled by indirect integration of venous return, which varies hydraulic pump output. Present cardiac output is six liters per side, with a power requirement of 20 to 32 watts.

The heart has functioned extremely well in short-term laboratory tests on canines and ruminants. Normal pressure and flows are maintained without difficulty. Hepatic or pulmonary congestion has not occurred. Air embolism, a problem in early experiments, has been solved by raising venous pressure before starting the artificial heart. Long-term implantation is now planned.

Cardiac Performance During Exercise Following Total Correction of Tetralogy of Fallot

John Burris, M. J. Jesse, Sidney Blumenthal, and James R. Malm, New York, New York

In the past five years, the operative mortality following total correction of tetralogy of Fallot at a medical center has been 5% (5 of 92). An additional 3% (3 of 92) have died after hospital discharge. Cardiac catheterization in 51 patients has documented resting hemodynamics following total correction (no intracardiac shunt and right ventricle [RV] to pulmonary artery [PA] gradient of less than 25 mm Hg). In this study, cardiac performance was assessed in six patients whose defects had been repaired from one to three years previously. At the time of study, all patients had systolic murmurs at the left base; three had diastolic murmurs compatible with pulmonic insufficiency. None of these patients had intracardiac shunts as determined by hydrogen-sensitive catheter. Five of the six patients had resting RV to PA gradients of 25 mm Hg or less. One patient had a resting gradient of 40 mm Hg. Measurements were made at rest and during exercise (300 kg-m/min) of: pulmonary artery, right ventricular (RVSP, RVED), and brachial artery pressures. Cardiac index (CI) was determined by dye-dilution curve, using indocyanine-green indicator. All six patients increased their CI normally with exercise. Four patients increased the RV to PA gradient by 15 mm Hg or more during exercise. Increases in RVED occurred during exercise in three patients. The data indicate that these patients respond to exercise with normal cardiac output. With respect to pressure, they respond much like patients with mild pulmonic stenosis.

Hypovolemic Shock Following Inferior Vena Caval Ligation

John L. Cahill, Nicholas Tilney, and Edward A. Edwards, Boston, Massachusetts

The in-hospital mortality rate in a consecutive group of 82 patients undergoing caval ligation has been 21% (17 patients). Four patients died, while 17 recovered from a syndrome of hypotension and oliguria and massive lower-extremity swelling, occurring within 24 hours postoperatively. Deaths in the other 13 patients were attributed to such causes as myocardial infarction or congestive heart failure, but hypovolemic shock was often significant in their deterioration.

Two indices have been particularly useful in early recognition of this syndrome. Close observation of the hourly urinary volume is important; unless its decrease is offset by replacement of intravenous colloid, the patient may develop acute tubular necrosis. Secondly, serial circumferential measurements of the lower extremities must be taken. As large amounts of plasma sequester in pelvis and limbs through massive venous thrombosis distal to the ligature, these measurements call attention to the quantity of colloid lost. Local compression, heparin, and elevation aid in controlling this swelling.

Recognized early, the syndrome responds well to plasma volume support. It is helpful to monitor patients with cardiovascular instability, both prior to and following operation, with serial plasma volumes and central and peripheral venous pressure determinations.

Evaluation of the Currently Accepted Electrocardiographic Criteria for P Mitrale and Left Atrial Enlargement in Sixty-two Patients with Surgically Proven Mitral Stenosis

Juan B. Calatayud, John L. Saunders, Washington, District of Columbia, Vladir Maranhao, Philadelphia, Pennsylvania, Patrick A. Gorman, Washington, District of Columbia, Klaus J. Schulz, Neptune City, New Jersey, and Harry Goldberg, Philadelphia, Pennsylvania

A group of 62 patients, average age 38.3 years, with significant mitral stenosis in sinus rhythm underwent open-heart surgery for mitral valvotomy. The electrocardiogram and the chest X-rays nearest to the operation were studied in all cases.

The amount of left atrial enlargement (LAE) detected by X-rays or directly visualized at surgery was graded from 1 to 4. In 28 cases, grade 3 or 4 LAE was present by X-rays or visual inspection or both. In six cases, no LAE could be detected by either method.

Currently accepted ECG criteria for P mitrale and LAE were tested against the total group of 62 patients (A) and against the group of 28 (B) with grade 3 or 4 LAE. The P-wave duration in the frontal plane was 0.12 second or more in 38 (61%) in group A, while 21 cases (75%) satisfied the criteria in group B. The criterion of a negative P deflection in V_1 equal to 0.06 second or more and -0.10 mv or greater was satisfied in 50% of group A and in 57% of group B patients. The criterion of P terminal force of 0.03 or more (the product of the amplitude of the negative component of the P in V_1 and its duration, as defined by Morris) was satisfied in 68% of group A and 82% of group B subjects. Other criteria were tested but were less satisfactory than those mentioned.

Of the ECG criteria for P mitrale and LAE, a P duration in the frontal plane of 0.12 second or more and the criteria of Morris appear to correlate best with the presence of significant LAE in this group of patients with proven mitral stenosis.

Electrocardiogram in Congenital Defect of the Pericardium

John A. Callahan, James C. Broadbent, Owings W. Kincaid, and F. Henry Ellis, Jr., Rochester, Minnesota

Congenital defect of the pericardium was first recognized at postmortem examination in 1788. There have been relatively few cases described since then, mostly those observed at thoracotomy. This anomaly has been mistaken for various cardiac malformations and has led to unnecessary restrictions. Rarely, the circulation has been seriously embarrassed by herniation of a portion of the heart through the defect.

This anomaly was observed at thoracotomy in six patients and demonstrated by artificial left pneumothorax in one patient. All defects were left-sided and six were large. In five patients without associated heart disease, the mean QRS vector in the frontal plane ranged between $+60°$ and $+130°$. In four patients, it was $+90°$ or greater. There was leftward displacement of the transition zone in the precordial leads in all. No evidence of right ventricular enlargement was present, and the atrioventricular and intraventricular conduction were normal. It is postulated that these electrocardiographic observations are characteristic of the unusual position of the heart in the thorax permitted by the absence of a restraining pericardium.

Although a rare condition, absence of the pericardium has been diagnosed ante mortem in 29 instances since 1936. The roentgenologic observations in this condition are becoming well known and, with the electrocardiographic characteristics described above, should provide the basis for more definitive study.

Hyperuricemia in Essential and Renal Hypertension (P)

Paul J. Cannon, William B. Stason, Felix E. Demartini, Sheldon B. Sommers, and John H. Laragh, New York, New York

Forty-seven per cent of 217 hypertensive patients were hyperuricemic (females >5.9 mg%; males >6.4 mg%): 43% of 141 patients with primary, 44% of 52 with renal, and 75% of 24 with malignant hypertension. Among untreated patients, the incidence of hyperuricemia increased with blood urea nitrogen (BUN) >22 mg%, rising in primary hypertension from 22% (12/54) to 73% (7/11) and in renal hypertension from 14% (3/21) to 63% (10/16). No correlation existed between hyperuricemia and duration of disease, height of blood pressure, or serum [K^+]. The incidence of hyperuricemia was slightly increased in those with hypercholesterolemia ($>$ 240 mg%). Thirty-eight per cent of untreated patients were hyperuricemic (45/119); hypotensive therapy increased this to 58%. Thiazides in primary hypertension increased the incidence to 63% (31/49) and other antihypertensive drugs to 47% (20/42). Significant lacticacidemia occurred in 96 patients (mean 24 mg% versus 16 mg% control). No direct correlation between venous

serum levels of lactic and uric acids was found in 21 untreated patients with primary hypertension. Since a high incidence of hyperuricemia was found in both primary and renal hypertension, the data suggest that it does not result from overproduction of uric acid genetically linked to primary hypertension. The increased incidence with azotemia or antihypertensive therapy suggests reduced renal excretion. Kidney sections from selected hyperuricemic hypertensive patients demonstrated glomerulosclerosis and Henle loop alterations similar to gouty kidneys. These changes, plus demonstration of uric acid deposits in renal medullary tissue, raise the possibility that hyperuricemia may contribute importantly to the renal damage which accompanies hypertensive disease.

Hypocholesterolemic and Uricosuric Properties of Hepatocatalase Peroxidase (H-Peroxidase)

Josefina Caravaca, Carlos A. Velasco, Horacio Orejarena, and E. Grey Dimond, La Jolla, California

Lyophilized bovine hepatocatalase lowers serum cholesterol in experimental animals and in humans, while crystalline hepatocatalase with much higher catalatic activity has little or no effect. The hypocholesterolemic action of lyophilized hepatocatalase was found to be related to a state of partial dissociation to smaller subunits with peroxidatic activity, but devoid of catalatic action.

This report deals with the isolation of an active peroxidase (H-peroxidase) as a molecular subunit of hepatocatalase and its evaluation as a hypocholesterolemic and uricosuric agent in experimental animals. H-peroxidase was obtained as a stable powder from both crystalline and lyophilized hepatocatalase preparations by alkaline hydrolysis, dialysis, and lyophilization, and its effect on serum lipids, beta/alpha-lipoprotein ratio, uric acid, and aortic cholesterol studied in normal and hypercholesterolemic rabbits.

In normal rabbits, serum lipids, beta/alpha-lipoprotein ratio, and uric acid were significantly reduced after two weeks of daily treatment with 300 units of H-peroxidase. Average values from 12 animals were: cholesterol, control (C) 44 mg%; H-peroxidase treated (H-PO) 25 mg%; phospholipids, C 96 mg%, H-PO 75 mg%; triglycerides, C 85 mg%, H-PO 33 mg%; beta/alpha-lipoprotein ratio, C 2.09 mg%, H-PO 1.31; uric acid, C 366 μg%, H-PO 246 μg%. No toxic, allergic, or immunological reactions were observed. Treatment with H-peroxidase significantly reduced aortic cholesterol deposition in rabbits fed a high-cholesterol diet for 12 weeks. Average cholesterol values (mg% dry tissue) from ten controls and ten treated animals were: C, 5.2; H-PO, 1.9. These results suggest the potential pharmacological value of H-peroxidase in the control of cholesterol and uric acid metabolism.

Left Atrial Contribution to Ventricular Performance in Mitral Stenosis

Richard A. Carleton, Mitchell Passovoy, and John S. Graettinger, Chicago, Illinois

Previous observations in patients with mitral valvular disease, which showed insignificant increases in cardiac output when atrial fibrillation was converted to sinus rhythm, suggested that left atrial systole made only a small contribution. Two groups of patients were studied at various paced ventricular rates (VR): 12 with heart block without valvular disease (42 paced rates) and 3 with mitral stenosis (6 paced rates; mitral areas less than 1.1 cm^2). Since average peak aortic systolic pressure correlated highly with average stroke output (Fick) in patients studied at more than 3 VR, peak aortic systolic pressure (PASP) was used as an index of beat-to-beat changes in stroke output. A parabolic relationship between PASP and P-R at each VR permitted statistical estimation of each optimal P-R interval at which PASP was highest. The least effective P-R intervals were those at which PASP was lowest. Optimal P-R was inversely related to VR ($r = -0.89$).

In the 12 patients, atrial contribution, expressed as the percentage increment of PASP at each optimal P-R above the lowest PASP values, was significantly related to VR ($r = +0.79$); at rates of 35 to 59, the contribution was $8.9 \pm$ SE 1.3%; at 60 to 89, 18.9 ± 1.6%; and at 90 to 125, $26.8 \pm$ 2.2%. Two patients with mitral stenosis, studied at a VR of 100, had atrial contributions of only 7 and 11%. The third, studied at VR of 60, 80, 97, and 120, had no atrial contribution above 12%. Mitral stenosis significantly reduced left atrial systolic effectiveness ($P < 0.01$) and the hemodynamic importance of sinus rhythm.

Diabetic Angiopathy Studied by Pedal Angiography (P)

Anthony J. Carnazzo,‡ Gerard J. Kelly, Hugh S. Levin, Vincent Runco, and Richard W. Booth, Omaha, Nebraska

An angiographic method was developed in our laboratory to demonstrate for the first time in vivo pathological changes in small peripheral arteries of diabetic patients, to elucidate the natural history of the process, and to help determine the correct amputation level when gangrene is present. The preliminary films and angiographic series are obtained with the patient supine, hips and knees flexed, and feet flat on the anteroposterior Schonander cassette changer. Low spinal

anesthesia is used to prevent pain-induced lower-extremity motion from contrast-media injection. Following percutaneous femoral arterial catheterization, radiopaque dye is injected under pressure into the superficial femoral artery for unilateral angiograms, or into the terminal aorta for bilateral studies. Initiation of the exposure sequence of 2 films/sec for 13 seconds is judged by a previously determined catheter tip–to–pedal artery radioisotope transit time. Arterial, capillary, and venous phases are visualized on the angiograms.

Changes in diabetic subjects without peripheral gangrene included: (1) a sparsity of demonstrable pedal and digital arteries; (2) beading and tortuosity of dye-filled vessels; and (3) small, irregular, filling defects in otherwise normal or tortuous vessels. Observations in the presence of gangrene included: (1) no demonstrable blood supply to gangrenous tissue; (2) an abundance of rapidly filling, dilated, small arteries in the area of surrounding inflammation; and (3) a subsequently occurring abnormal capillary blush followed by rapid venous filling. Minimal amputations have been performed in six diabetic patients after adequate proximal pedal blood supply was demonstrated angiographically. Prompt primary healing occurred in all patients.

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery: Certain Therapeutic Considerations (P)

Aldo R. Castaneda, Robert A. Indeglia, and Richard L. Varco, Minneapolis, Minnesota

When the left coronary artery arises anomalously from the pulmonary artery, pathological, hemodynamic, and clinical evidence indicates that blood flow in this anomalous left coronary artery is toward the pulmonary circulation, thus establishing a true coronary arteriovenous fistula.

Of nine cases reviewed, four died without operative intervention from causes directly related to this congenital fistula. Four other children ranging in age from two months to seven years underwent surgical ligation of the left anomalous coronary artery at its junction with the pulmonary artery and all lived. One additional child died during induction of anesthesia. There has been no other operative or late death.

Follow-up ranges from 7 to 24 months. Various salient diagnostic features were studied, including vectorcardiographic and electrocardiographic evidence of left ventricular hypertrophy and strain, with Q- and T-wave changes in leads I, aV_L, V_5, and V_6, as well as ready demonstration of the coronary fistula and the left-to-right shunt by retrograde aortography.

The Wendensky Effect: Clinical Application

Agustin Castellanos, Jr., Louis Lemberg, Douglas Johnson, Miami, Florida, and Barouh Berkovits, Chelsea, Massachusetts

In the nerve muscle preparation, Wendensky demonstrated that subthreshold stimuli became threshold following an impulse of high intensity. The Wendensky phenomenon was investigated by intracardiac electrical stimulation in seven patients with complete or advanced atrioventricular block. Ventricular excitability was studied with the aid of two artificial pacemakers connected to a specially constructed tetrapolar catheter electrode. The pacemakers delivered underdamped 2.5-msec pulses, with voltages ranging between 0 and 25.

A supernormal phase lasting 160 to 195 msec was recorded in four cases. In two patients, subthreshold impulses produced artificial beats only after the strong stimuli. This occurred only when the intensity of the stimulus was increased to five and a half and seven times threshold, respectively. Vulnerability and supernormality were not the underlying mechanisms, since the responses were seen as late as 300 msec after the end of the preceding T wave. The mechanism by which the effects of stronger stimuli allow previous subthreshold impulses to become threshold is explained by assuming that the electrical impulses cause a prolonged lowering of the threshold during the complete recovery period (the period following the supernormal phase). It is suggested that the Wendensky effect explains the genesis of extrasystoles occurring late in diastole, without implying a re-entry phenomenon.

Hazard of Ventricular Fibrillation from Paired Pulse Stimulation (P)

C. Hilmon Castle and Leland S. Briggs, Salt Lake City, Utah

Paired-pulse stimulation (PPS) has been used to potentiate myocardial contraction, to slow ventricular rate, and to facilitate coronary angiography by lowering arterial pressure transiently. It has been reported that the level of direct current required to produce ventricular fibrillation (VF) is 20 to 30 times the minimal stimulating level, and the inference is that there is no hazard of VF from commercially available PPS units, even when the stimulus occurs in the vulnerable zone (VZ).

VF was consistently induced in ten anesthetized dogs by PPS with a commercially available paired-pulse pacemaker with a maximum amplitude of 12 volts. Electrical impulses of 2-msec duration were delivered to the myocardium via a transvenous bipolar catheter in the right ventric-

ular cavity. Minimum stimulus to depolarize the ventricles in the excitatory phase was 1 volt (± 0.2 volt) by this technique. To induce VF by a single stimulus in the vulnerable zone, 20 to 30 times the minimum stimulus was required; however, when the first impulse of PPS occurred in the VZ and the second 90 to 110 msec later, VF could be produced in all dogs at significantly lower levels (range, 4 to 12 volts).

These observations emphasize the potential hazard of VF from PPS, even with stimuli of relatively low amplitude. If this method of stimulating the heart is to be used, the well-defined VZ of the electrical cycle should be avoided and no more than the minimum stimulus required to depolarize the ventricles in the relative refractory period used.

Variables Affecting Splitting of the Second Heart Sound in Atrial Septal Defect (P)

Robert F. Castle, Chapel Hill, North Carolina

Many observers have related the degree and lack of respiratory variation in second heart sound splitting in atrial septal defect to the size of the left-to-right shunt. In order to test this proposed relationship and to study other variables which may influence splitting, phonocardiograms obtained during normal respiration were analyzed in 42 patients, ranging between 18 months and 25 years of age, with ostium secundum defects. No patient had elevated pulmonary vascular resistance. In all subjects, the relationship of pulmonary to systemic flow (Qp:Qs ratio) was determined; this ratio ranged between 1.5 and 7.6.

The influence of age, indexed size of the defect (Qp:Qs ratio), and heart rate on mean splitting of the second sound was analyzed by the method of multiple linear regression, using the UNIVAC-1105 computer.

No correlation was found between mean splitting and indexed shunt size. However, a positive correlation ($r = 0.59$: significant at $\alpha = 0.01$) was observed between age and mean splitting. An inverse correlation was noted between heart rate and splitting ($r = -0.49$: significant at $\alpha = 0.05$). The respiratory variability in splitting did not change with age or correlate with shunt size. Eleven of 42 patients (26%) had 0.015-second or greater respiratory variation in splitting.

This study indicates that with pulmonary to systemic flow ratios of 1.5 or greater, neither the degree of mean splitting nor the absence of significant respiratory variation correlates with shunt size. Further, in young children, normal splitting does not exclude the presence of an atrial septal defect.

Synchronous Pacing of the Heart: Three Years' Clinical Experience (P)

Sol Center, Miami, Florida, and David A. Nathan, Miami Beach, Florida

Synchronization of the atrium and ventricle in man by means of an implantable cardiac pacer has been accomplished since June, 1962. Among 21 patients with complete heart block or arrhythmias resulting in Stokes-Adams attacks, an increase in the cardiac index at increasing ventricular rates was demonstrated in the majority. The feasibility of long-term pacing was proven by repeated measurements of atrial voltage and ventricular threshold. A high incidence of pacer failure in the early series has been reduced by improvements in packaging techniques.

Thirty-six patients with complete heart block have had the "new" synchronous pacer implanted. One postoperative death occurred, three weeks after pacer implantation, from duodenal ulcer hemorrhage. Failure of the pacer itself, manifested by loss of ventricular capture, has occurred in two patients. Fracture of a platinum electrode has occurred in one. Elgiloy electrodes are being used exclusively at present. Pacer pocket infections have occurred only in those patients who have undergone reimplantations. Dramatic rehabilitation has been observed in all survivors. In the event of the return of normal sinus rhythm (15 of 35), the pacer follows but does not interfere with normal conduction. Contraindications to the use of synchronous pacers are atrial fibrillation or atrial bradycardia.

Effect of Head-up Tilt on Pulmonary Blood Volume in Normal Subjects and Patients with Congestive Heart Failure

William R. Chaffee, John F. Keighley, Harold Smulyan, and Robert H. Eich, Syracuse, New York

The effect of 45° head-up tilt was investigated in seven subjects without known cardiac or pulmonary disease. Cardiac output (CO) was measured by interrupted arterial sampling of I^{131}-iodopyracet before and after tilting. Scintillation counters over the right and left sides of the heart recorded the mean transit time of the indicator. The product of the difference in mean transit time and the cardiac output is a measure of pulmonary blood volume (PBV), which includes a portion of the cardiac volume.

With tilting, cardiac index fell in all (mean, -1.15 L/min/m^2 $\pm$ 0.49) and PBV fell in all (mean, 171 ml/m^2 $\pm$ 76). Nine patients with congestive heart failure due to arteriosclerotic heart disease were studied in the same manner. All were compensated to the extent that they could

lie flat for the ten-minute equilibration period. In these patients, tilting produced a fall in cardiac index in eight of the nine (mean, -0.35 L/min /$m^2 \pm 0.32$) and PBV fell in five of the nine (-43 ml/$m^2 \pm 85$).

The fall in CO and PBV is significant in the normal subjects. Although the decrease in CO is significant in the subjects with congestive failure, the fall was only one-third of that seen in normal subjects. The change in PBV was not significant. It is postulated that in the patients with congestive failure, high venous tone prevents venous pooling and a fall in cardiac output. Without a fall in output, pulmonary blood volume does not fall significantly.

Clinical Experience with an Implanted Pacemaker-Catheter Electrode System

William M. Chardack, Anthony J. Federico, Andrew A. Gage, Buffalo, New York, and Wilson Greatbatch, Clarence, New York

A bipolar catheter electrode has been designed for long-term intracardiac use in combination with a subcutaneously implanted pacemaker. The electrical conductors are two stainless steel coils in separate channels of a silicone rubber double-lumen tube. Terminal contacts are made of platinum. The coils admit stylets for stiffness and curvature during placement into the trabeculae of the right ventricular apex. After positioning, the stylets are withdrawn, leaving a flexible and soft structure. The catheter is preferentially introduced into the right external jugular vein. If this site is unavailable, the left external or internal jugulars may be used. The pulse generator is placed subcutaneously below the clavicle. The procedure requires only local anesthesia, thoracotomy is avoided, and anticoagulants are not needed.

Since December 1963, 20 patients have been treated with this system. Early in the series, fracture and stiffness of the stylets, which then had been only partially withdrawn, caused four complications. Early perforation (one), late perforation (one), and disruption of a coil (two) required three thoracotomies for placement of myocardial electrodes, with one postoperative fatality from mesenteric thrombosis. Nineteen patients are currently pacemade (1 to 17 months). Ten have been followed from 6 to 17 months (mean, nine months). No complications have occurred since complete withdrawal of the stylets has been adopted. This approach seems to be particularly suitable for poor-risk patients and when failure or infection of an implanted system (with myocardial electrodes) would require another thoracotomy.

Hemodynamic Consequences of Instant Reversion of Atrial Fibrillation and Flutter to Sinus Rhythm

Tsung O. Cheng, Brooklyn, New York

Previous studies on the hemodynamic effects of reversion from atrial fibrillation and flutter to sinus rhythm all suffered three disadvantages: (1) the antiarrhythmic drugs themselves had profound influence on cardiodynamics; (2) variable and usually long intervals often elapsed between studies; and (3) heart rate often differed significantly between studies. Transthoracic direct-current countershock offered an excellent opportunity for studying the hemodynamic consequences of instant reversion of atrial fibrillation and flutter to sinus rhythm.

In patients with mitral valvular disease, cardiac output increased after reversion to sinus rhythm both at rest and during exercise. This beneficial effect of reversion was either less obvious or absent following successful mitral valvuloplasty. Results in patients with hypertensive cardiovascular disease and coronary arterial disease were less spectacular. Following reversion, patients with idiopathic atrial fibrillation showed no significant changes in cardiac performance; pressures in both systemic and pulmonary circuits showed variable changes.

Electrical reversion provided a unique opportunity for studying the cardiovascular response to exercise in patients with atrial flutter and regular ventricular response. In these cases, an increase in cardiac output during exercise was achieved solely by an increase in stroke volume. However, when sinus rhythm returned, the increase in cardiac output during exercise was achieved primarily through an increase in heart rate. Thus, the body's primary homeostatic mechanism in response to exercise was an increase in heart rate; when a rise in heart rate could not occur, a reserve mechanism of increasing stroke volume was called upon to meet the need of an increased cardiac output.

Left Ventricular Circumference Changes with Hemodynamic and Inotropic Interventions

Horacio E. Cingolani, Roger R. Taylor, Robert H. McDonald, Jr., and Joseph P. Gilmore, Bethesda, Maryland

It has been reported previously that during isovolumic systole, left ventricular circumference increases, followed by a decrease during ejection and a further decrease after aortic valve closure. There are, however, few data available to indicate the extent to which ventricular circumference is influenced by hemodynamic and inotropic

changes. By right-heart bypass and isolated supported heart preparations, the influence of changing stroke volume, aortic pressure, or the administration of inotropic agents on left ventricular circumference, as measured by a mercury-in-rubber gauge, could be determined. When stroke volume was increased at constant mean aortic pressure and heart rate, the fraction of total circumferential shortening which occurred during ventricular ejection increased. The reverse held when aortic pressure was increased while stroke volume and heart rate were maintained constant. This difference between the response of shortening to aortic pressure and stroke volume occurred when ventricular end-diastolic pressure was increased to the same extent. An increase in aortic pressure or stroke volume diminished the extent of the increase in circumference seen during isovolumic systole.

The heart in failure (low stroke volume, high left ventricular end-diastolic pressure) showed a pattern of circumferential changes during shortening similar to that seen when left ventricular end-diastolic pressure was increased by increasing stroke volume in the nonfailing heart. When digitalis was administered to the failing heart, isovolumic shape changes became more prominent. Digitalis and other inotropic agents produced changes in circumference during shortening similar to those produced by increased aortic pressure. The results show that changes in the shape of the heart during the cardiac cycle are modified by hemodynamic and inotropic conditions.

Experimental Study and Clinical Use of Epinephrine for Treatment of Low Cardiac Output Syndrome (P)

Laurence H. Coffin, Jr., Jay L. Ankeney, and Edward M. Beheler, Cleveland, Ohio

The metabolic, cardiotonic, and peripheral vascular responses to epinephrine were studied in 20 animal experiments. Portal and arterial pressure, weight, peripheral and splanchnic venous return, and changes in arterial pH, O_2 content, CO_2, glucose, lactate, and pyruvate were measured during a three-hour period. Epinephrine, in doses of 0.5 to 2.0 μg/kg/min, was administered to ten animals in which the heart and lungs were bypassed with an oxygenator at a fixed flow rate of 100 ml/kg/min. In a second group of ten animals, the effect of epinephrine on the intact circulation was studied.

With a fixed cardiac output (bypass), 0.5 μg/kg/min caused a significant rise in peripheral resistance, with a rise in mean splanchnic flow from 735 to 822 ml/min and a fall in peripheral flow from 1,467 to 1,365 ml/min. With an intact circulation, 1.0 μg/kg/min raised mean cardiac output from 2,001 to 2,346 ml/min, splanchnic flow from 620 to 757 ml/min, and peripheral flow from 1,379 to 1,592 ml/min without a significant rise in calculated peripheral resistance. Higher doses increased resistance but not flow. Significant formation of excess lactate was noted only in dogs with intact circulation, in spite of measured increases in blood flow and tissue oxygen consumption.

A continuous infusion of epinephrine (0.1 to 0.5 μg/kg/min) was administered to 20 postoperative patients with low cardiac output syndrome. Initially, all patients responded with an increase in blood pressure, improvement in peripheral circulation and urinary output. Twelve patients survived, whereas eight eventually failed to respond and died.

A Simple, Objective Test for Intermittent Claudication (P)

Jay D. Coffman and John A. Mannick, Boston, Massachusetts

An objective test is needed to demonstrate the deficit in muscle blood flow during exercise in patients with intermittent claudication. The radioisotope disappearance rate from exercising muscle was evaluated in subjects with and without arteriosclerosis obliterans (ASO). NaI^{131} was injected into the gastrocnemius muscle of standing subjects. Disappearance rates were recorded during and following two minutes of regulated exercise. Disappearance rates are expressed as half-times (t/2).

In subjects *without* ASO, exercise t/2 averaged 1.8 minutes; postexercise t/2 was 2.8 minutes. In 16 patients with intermittent claudication, arteriography demonstrated obstructed superficial femoral arteries. In eight, the disappearance rate stopped completely during exercise. In the remaining eight patients, exercise t/2 averaged 10.3 minutes. Postexercise t/2 for the group averaged 3.8 minutes. Exercise tests were also performed in ten patients with clinical evidence of femoral artery blocks (no X-rays). In four, the disappearance rate stopped during exercise; in six, exercise t/2 averaged 6.8 minutes; postexercise t/2 in this group averaged 3.8 minutes. An abnormal test was accepted as having: (1) a four-minute or longer exercise t/2 (normal ranged to 3.5 minutes); and/or (2) a shorter t/2 after than during exercise.

In 13 of the patients who had arteriography, grafts were inserted to bypass the arterial obstruction. Postoperatively, exercise t/2 averaged 2.1 minutes; postexercise t/2, 2.5 minutes.

The exercise radioisotope test yields objective evidence of the muscle blood flow deficit in ASO. It is a simple, valuable diagnostic procedure suit-

able for screening patients, and is useful in demonstrating results of treatment.

Mechanism of Disappearance of Korotkoff Sounds in Clinical Shock (P)

Jay N. Cohn and Robert C. Daddario, Washington, District of Columbia

Brachial arterial pulsations and auscultatory blood pressure may be greatly reduced or absent in clinical shock, despite normal intra-arterial pressure. A false impression of hypotension may lead to serious errors in therapy. In 31 patients with shock or hypotension, the discrepancy between direct systolic arterial pressure (SAP—strain gauge) and indirect systolic (cuff) pressure was directly related to total peripheral vascular resistance (PVR). Among 18 patients with PVR greater than 1,500 dynes sec/cm^5, six had no auscultatory or palpatory brachial pressure, although SAP varied from 84 to 164. In the other 12 patients, SAP was significantly higher than cuff pressure, the difference averaging 23 mm Hg. In 13 patients with PVR less than 1,500 dynes sec/cm^5, a significant discrepancy was present in only three, SAP averaging only 3 mm Hg more than cuff pressure.

The mechanism of disappearance of the Korotkoff sounds was studied in normal subjects. Forearm blood flow (FBF) was measured by venous occlusion, using a Whitney gauge; brachial arterial pressure was recorded by a strain gauge; and Korotkoff sounds were recorded in the same arm with a microphone, amplifier, and recorder. Infusion of *l*-norepinephrine into the axillary artery in doses insufficient to raise arterial pressure produced a progressive decrease in FBF, associated with diminution and finally disappearance of the Korotkoff sounds, although direct brachial arterial pressure was unchanged.

It is concluded that the Korotkoff sounds are blood flow dependent, and that reduced forearm blood flow in patients with severe peripheral vasoconstriction makes indirect blood pressure measurement unreliable.

Surgery for Mitral Valvular Disease During Childhood and Adolescence (P)

Harold A. Collins, Rollin A. Daniel, Jr., H. William Scott, Jr., and Francis A. Puyau, Nashville, Tennessee

Congenital and acquired lesions of the mitral valve can produce symptoms of sufficient severity during the first two decades of life to warrant operation. During the past eight years, 25 patients under the age of 21 have received surgery for mitral valvular disease.

Sixteen patients had rheumatic mitral stenosis, and one patient had congenital mitral stenosis. The age range was from 8 to 20 years. Pulmonary hypertension was an almost constant finding in those patients who had cardiac catheterization. Transatrial or transventricular fracture of the mitral valve was possible for 15 patients, but open cardiotomy was necessary for two patients. Microscopic examination of the atrial appendage revealed an unexpectedly high incidence of active myocarditis. No patient died as a result of operation. All but three patients have had sustained improvement postoperatively.

Eight patients, ranging in age from 6 to 18 years, had surgery for severely incapacitating mitral insufficiency; the lesion was congenital in two of the patients. Mitral annuloplasty was utilized in two early patients, both of whom succumbed. Replacement of the mitral valve with a Starr prosthesis of adult size was accomplished in the other six patients. Four of these patients survived and are greatly improved. The two deaths occurred in patients with coexistent cardiac lesions which were simultaneously corrected.

This study indicates the feasibility and generally good results following surgery for severe mitral valvular disease during childhood and adolescence.

Plethysmographic Evaluation of Upper Extremity Hemodynamics in the Subclavian Steal Syndrome (P)

Margaret C. Conrad,‡ James F. Toole, and Richard Janeway, Winston-Salem, North Carolina

Studies of four patients with subclavian steal syndrome have been made. Digital flow, digital artery systolic pressure, resistance, pulse volume, pulse contour, and delay between right and left digital pulses were evaluated preoperatively in all patients and following surgical reconstruction of the proximal subclavian artery in cases selected for repair. Digital artery pressure was consistently lower in the digits on the side of the subclavian occlusion than in those of the normal arm. However, flow in the digits of the affected extremity was equal to or higher than that in the opposite side, except when a second, more distal, occlusion was present. This suggested a compensatory dilatation of the skin bed in response to the subclavian occlusion. In each case, there was a slight delay in the foot of the digital pulse on the occluded side and a more marked delay in the peak. Distal to the occlusion, the pulse amplitude was decreased relative to the flow and the pulse contour was damped in appearance. With exercise of the arm with proximal subclavian occlusion, the digital pulse decreased to about one-third of its pre-exercise value (confirming the clinical observation that

radial pulse decreases or disappears with exercise on the side of occlusion), and there was a small decrease in the amplitude of the digital pulse in the opposite extremity. Following reconstruction of the subclavian artery, all parameters returned toward normal except when a second, more distal, occlusion was present.

New Enzyme Tests in Detection of Myocardial Infarction

Eugene L. Coodley, Los Angeles, California

As a result of the lack of specificity of current diagnostic modalities in the detection of myocardial infarction, a search for newer procedures has been undertaken. Presently employed enzyme procedures have the disadvantage of being influenced by many factors and disease processes outside of the heart, and electrocardiographic diagnosis may not be obtainable in diaphragmatic or intramural infarctions, or when prior tracings have shown abnormalities.

A study of the value of creatine phosphokinase and hydroxybutyrate dehydrogenase compared with serum transaminase, lactic dehydrogenase, and other laboratory criteria of infarction has been conducted in 79 patients. Patient diagnoses have included infarction, chronic heart disease, and noncardiac disease affecting serum enzymes.

A higher degree of positivity was obtained with the newer enzyme procedures in the presence of acute infarction than with either current enzyme procedures or other laboratory methods. The newer enzymes are not affected by most of the conditions which influence transaminase and lactic dehydrogenase. Creatine phosphokinase was demonstrated to be the most valuable enzyme early after infarction, and gives false-positive reactions only in hypothyroidism, muscle disease, and cerebral infarction. Hydroxybutyrate dehydrogenase proved highly specific, and persisted for over two weeks in most cases. The differentiation between reinfarction and heart failure was facilitated by these enzymes.

Experience with Double-Caged Ball-Valve Prostheses for Cardiac Valve Replacmeent

Denton A. Cooley, Arthur C. Beall, and Grady L. Hallman, Houston, Texas

For most patients with advanced acquired valvular disease, total excision with valve replacement offers the only means of relief of symptoms and restoration of physical activity. Development of caged-ball prostheses more than four years ago provided the first effective means of surgical treatment in such patients. Since April 1, 1962, caged-ball prostheses have been used for more than 600 patients with acquired valvular heart disease requiring valve replacement in this center. Cardiopulmonary bypass for these procedures has been conducted using disposable plastic oxygenators primed with 5% dextrose in distilled water under normothermic conditions. Although results have been gratifying, with a surgical mortality rate of approximately 15%, the need for a better prosthesis has been evident to eliminate some of the complications such as thromboembolism and problems concerned with poor function of the prosthesis.

Recent experience with 100 patients in whom double-caged ball-valve prostheses have been used suggests distinct advantages of this type of valve over other types of caged-ball prostheses used previously. Early results reveal a reduction in morbidity and mortality associated with arrhythmias and thromboembolic phenomena. Fifty-eight of these patients required aortic valve replacement, 32 required mitral valve replacement, and 10 required double valve replacement.

Biocellular Approach to the Treatment of Digitalis-Toxic Arrhythmias with Diphenylhydantoin, Citrate Salts, Beta-Adrenergic Blocking Agents, and Ajmalin (P)

Eliot Corday, Herbert Gold, Harold Bernstein, Tzu-Wang Lang, and Vaclav Bazika, Los Angeles, California

The agents listed above are most effective for the treatment of serious digitoxic arrhythmias. The authors studied the effects of these drugs in five series of 20 dogs each in which arrhythmias were created by a toxic dose of digitalis. The mortality rate of the control group was 60%. The mortality rate was reduced to 5% by diphenylhydantoin, to 10% by citrate salts, and to 15% by ajmalin (a Rauwolfia derivative). These agents all cause a change of cellular permeability to potassium and thus have a beneficial effect on the resting cell membrane potentials. Diphenylhydantoin, citrate salts, β-adrenergic blocking agents, and ajmalin are equally impressive for the treatment of the human patient suffering from digitalis toxicity.

Effects of Tolazoline on Pulmonary Circulation in Children with Hypoxic Pulmonary Hypertension (P)

Ernest K. Cotton, Leslie Kelminson, and John H. K. Vogel, Denver, Colorado

The purpose of this study was to evaluate the usefulness of tolazoline given acutely and chronically to children with hypoxic pulmonary hypertension. Five children, 4 to 12 years of age, with

cystic fibrosis and severe pulmonary involvement as shown by pulmonary function studies, and one subject, 16 years old, with restrictive chest disease, were studied. Right-heart catheterization was performed and observations made at rest, after tolazoline (T), 1 mg/kg into the pulmonary artery (PA), and with a combination of T and 100% oxygen. In five subjects, PA pressure (PAP) and response to T and O_2 were observed for periods ranging from three hours to four days following catheterization. This was achieved by floating a PE 50 or 60 tubing into the PA without fluoroscopy, either at the catheterization table or percutaneously at the bedside.

At rest, mean PAP ranged from 28 to 67 mm Hg, Sa_{O_2} from 61 to 79%, pHa from 7.250 to 7.407, and pulmonary vascular resistance (PVR) from 418 to 1,330 dynes-sec-cm^{-5}-m^2. Following T, PAP ranged from 16 to 38 and PVR from 230 to 530. This decrease in PAP was achieved without a significant change in either pHa or Pa_{O_2}. The addition of oxygen to T resulted in a slight further decrease in PAP, averaging 8 mm Hg. Repeated administration of T resulted in both progressively lower PAP and less tendency for PAP to return to control levels. Acute and chronic administration of tolazoline is effective in the reduction of hypoxic pulmonary hypertension without correction of pH or Pa_{O_2}.

Force-Velocity Relation During Single Isovolumic Left Ventricular Beats in the Assessment of the Contractile State of the Intact Heart

James W. Covell, John Ross, Jr., Edmund H. Sonnenblick, and Eugene Braunwald, Bethesda, Maryland

An inverse relation exists between force and velocity in the intact canine heart, and changes in this relation reflect alterations in the contractile state of the myocardium. A simplified technique was developed for determining force-velocity relations (F-VR) during single, isovolumic beats. The usefulness and sensitivity of this approach were studied by analyzing left ventricular (LV) performance in terms of the F-VR and the left ventricular function curve (LVFC) at control and at augmented levels of the contractile state, induced by small doses of norepinephrine (NE). Isovolumic contractions were produced by sudden inflation of a balloon in the aortic root during diastole. LV pressure and dp/dt were recorded, cardiac output was controlled by right-heart bypass, and LV volume was determined directly. For the LVFC, stroke work was calculated at various LV end-diastolic pressures, and for the F-VR, contractile element velocity and LV wall tension were calculated during isovolumic beats.

In all seven experiments, NE (0.01 to 0.14 μg/kg/min) always shifted the F-VR, with increases both in maximum velocity (average, 33.1%) and maximum tension (average, 16.9%). In contrast, in five experiments, no change in the LVFC was detectable, although in two, shifts upward and to the left occurred.

It is concluded that analysis of the F-VR during isovolumic beats permits practical application of the principles of muscle mechanics to the intact heart, and that small changes in myocardial contractile state can be detected. Furthermore, the F-VR may provide more sensitivity than the LVFC when such changes are reflected primarily in alterations in the velocity of myocardial contraction.

Metabolism and Distribution of Tritiated Quinidine

Lamar Crevasse, Yoshiharu Sako, and Myron Wheat, Gainesville, Florida

Tritium-labeled quinidine (Wilzbach method), 50 mg/kg per os, was given to mongrel dogs. Serum, urine, bile, and myocardial radioactivity were determined simultaneously.

In six acute experiments, serum levels of quinidine peaked in two hours, were accompanied by immediate appearance of urinary radioactivity which peaked in one to two hours, and accounted for the major excretory pathway. Biliary radioactivity was somewhat delayed, reaching a peak two to four hours after administration. Serum and myocardial levels of tritiated quinidine were correlated at 2, 4, 6, 12, and 24 hours following a single dose of quinidine. Serum levels fell in linear fashion, being 50% of the peak two-hour level in 24 hours. Despite falling serum levels, myocardial radioactivity peaked between four and six hours and exceeded serum activity one and a half times.

This study demonstrated that tritiated quinidine appeared immediately in the urine and that this was the major excretory pathway. The plateau of serum levels of quinidine at two hours was accompanied by peak biliary excretion and metabolism. Myocardial quinidine levels exceeded serum concentrations one and a half times.

Pressure Gradients Without Obstruction: A New Concept of Hypertrophic Subaortic Stenosis (P)

J. Michael Criley, Kenneth B. Lewis, Robert I. White, Jr., and Richard S. Ross, Baltimore, Maryland

Obstruction to outflow from the left ventricle has been considered an essential feature of hypertrophic subaortic stenosis. Although systolic pressure gradients within the left ventricle (LV) sup-

port this contention, a number of observations in patients with this disease are incompatible with significant obstruction: (1) the rate of rise of the arterial pulse is significantly higher than normal; (2) a normal stroke volume is present, and this volume is expelled more rapidly than normal; (3) the end-systolic cavity size of the LV is smaller than normal; and (4) obstruction is not often found at operation or autopsy in patients with high left ventricular gradients.

Left ventricular cineangiograms in eight patients with hypertrophic subaortic stenosis did not demonstrate obstruction at any site within the LV. Cinefluorographic recordings of catheter withdrawals through the LV, combined with the cineangiographic studies, permitted anatomical localization of the high-pressure areas in the LV. In each instance, high pressure was found when the catheter was in portions of the ventricular cavity which emptied completely in early systole. The outflow tract contracted only slightly, and the end-systolic cavity was confined to this area.

Isoproterenol infusions increased the rate and degree of LV emptying, thus obliterating portions of the LV cavity earlier, and increasing the peak pressure in the high-pressure areas.

It is concluded that contraction continues in areas of the ventricle which have been completely emptied in early systole, and that this phenomenon, rather than obstruction, is responsible for the pressure gradients within the LV in these eight patients.

Varying Arrhythmias Causing Adams-Stokes Syncope

Modestino G. Criscitiello and Robert A. O'Rourke, Washington, District of Columbia

A group of patients with Adams-Stokes syncope were followed by constant cardiac monitoring utilizing an instrument which could be set to record alterations in rate, rhythm, or QRS duration. Every syncopal episode was recorded electrocardiographically and the mechanisms involved were studied.

Six patients, previously "refractory" to medical therapy, were each found to have multiple arrhythmias producing Adams-Stokes syncope. Medical treatment often corrected one of the causal mechanisms but failed to prevent the others, or even served to precipitate them. Constant monitoring in three patients demonstrated arrhythmias amenable to appropriate medical therapy, and in three others showed the necessity for an intracardiac pacemaker. Arrhythmias documented at times of syncopal attacks included sinus bradycardia, paroxysmal atrial tachycardia, atrial fibrillation, and ventricular tachycardia, as well as varying degrees of atrioventricular block and ventricular asystole. Two uncommon mechanisms recorded were repetitive paroxysmal atrial tachycardia with long asystolic intervals and atrial tachycardia with repetitive concealed conduction.

Effects of Norepinephrine and Isoproterenol on Myocardial Performance in Experimental Cardiogenic Shock

Robert F. P. Cronin and Thomas Zsoter, Montreal, Quebec, Canada

The effects of norepinephrine and isoproterenol on myocardial performance have been studied in 20 closed-chest dogs after the production of shock by diffuse coronary embolization using plastic microspheres. Coronary blood flow (CBF) was measured by the I^{131}-iodoaminopyrine method, and myocardial oxygen uptake ($LVqO_2$) by simultaneous determination of the O_2 content of arterial and coronary sinus blood samples. Mean aortic pressure (MAP) and left ventricular end-diastolic pressure (LVEDP) were measured, and left ventricular work (LVW) and coronary vascular resistance (CVR) were calculated. Serial observations were also made of arteriovenous concentration differences of lactate and pyruvate across the myocardium. The average percentage changes 30 minutes after coronary embolization were: MAP, −39%; CBF, −29%; CVR, −6%; $LVqO_2$, −6%; and LVW, −41%; LVEDP rose an average of + 10 mm Hg.

Intravenous infusion of norepinephrine for 30 minutes in the dose range 0.2 to 0.8 μg/kg/min produced average percentage changes as follows: MAP, + 59%; CBF, + 73%; CVR, −2%; $LVqO_2$, + 44%; LVW, + 47%; and LVEDP, + 40%. At the conclusion of norepinephrine infusion, myocardial lactate extraction was markedly reduced in 14 of 20 animals and net lactate production was observed in the remaining six.

Infusion of isoproterenol in the same dose range produced almost as great an increase in LVW (average, + 35%) and $LVqO_2$ (average, + 31%). Increases in MAP and CBF were significantly less ($P < 0.1$), while LVEDP showed a highly significant fall ($P < 0.01$). Reductions in myocardial lactate extraction were significantly lower than during norepinephrine infusion. It is concluded that isoproterenol is superior to norepinephrine in its effect on myocardial performance in experimental cardiogenic shock.

Caged-Lens Prosthesis for Replacement of the Mitral and Aortic Valves

Frederick S. Cross and Richard D. Jones, Cleveland, Ohio

Although a silicone rubber–hinged lens valve has functioned well in dogs for periods up to

20 months, accelerated fatigue tests indicated weakness at the hinge, which precluded clinical use. This report describes a valve consisting of a lenticular closure within a titanium cage which offers several significant advantages. The lens requires a shorter excursion than does a ball of equivalent diameter, thus the cage may be made shorter (less than one-half the height of the ball cage). The reduced bulk of the cage permits insertion of lens prostheses with larger orifice size than is possible with the ball design. The silicone rubber lenticular closure, reinforced with a thin titanium ring, weighs only one-fourth to one-third as much as a ball of comparable diameter. The reduced mass of a lens compared with a ball decreases inertial effects during the opening and closing phases of valve function. Further dynamic advantage has been achieved by adjusting the density of the lens to approximately the specific gravity of blood. Pressure gradients measured across the lenticular valve are not different than those for a ball valve of equal orifice size at flow rates up to 40 L/min of water. Simultaneous left atrial and left ventricular pressure tracings and cineangiography demonstrate excellent function of the valve in vivo. The prosthesis has been used in six patients for mitral or aortic valve replacement. In each instance excellent valve function continues to the present time.

Diagnosis and Management of Massive Pulmonary Embolism (P)

George R. Daicoff, Klaus Ranniger, A. Gerson Greenburg, James J. Rams, and Peter V. Moulder, Chicago, Illinois

Massive pulmonary embolism still defies accurate clinical diagnosis and precise assessment of its severity, and the indications for pulmonary embolectomy are not clear. Clinical and experimental studies have therefore been undertaken to elucidate the diagnosis and proper management. Hemodynamic study has been completed in 50 dogs with massive repeated pulmonary embolization. Pulmonary arterial catheterization and arteriography have been performed in 15 seriously ill patients with a clinical diagnosis of possible pulmonary embolism. Two patients underwent successful pulmonary embolectomy and two patients underwent unsuccessful embolectomy. One patient underwent successful anticoagulation and fibrinolysis treatment of massive pulmonary embolism.

The following conclusions were apparent: (1) pulmonary arteriography can establish the diagnosis of massive pulmonary embolism in desperately ill patients without mortality and significant delay; (2) the degree of obstruction of the arterial bed as judged by arteriography and the systemic arterial, pulmonary arterial, and wedge pressure measurements indicate the severity of the embolization; (3) massive amounts of emboli can be lysed, as judged by serial pulmonary arteriography; (4) when the resting mean pulmonary arterial pressure is $39\% \pm 9\%$ of the mean aortic pressure in dogs, an additional 10-ml embolus is fatal, but not when the pulmonary arterial pressure is $26\% \pm 5\%$ of the aortic pressure; and (5) embolectomy can be successfully performed in the first few days of the disease and probably should be reserved for patients with a pulmonary arterial pressure 30% of their aortic pressure.

Serial Changes in Regional Blood Flow Following Experimental Pulmonary Embolism

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This study attempts to elucidate the immediate fate of embolized pulmonary vessels and serial changes in regional blood flow. Twenty-two anesthetized dogs were embolized with autologous blood clots and followed for periods up to seven days. After control selective pulmonary angiograms, 2 to 6 ml of autologous blood clot or radiopaque blood clot were injected into a jugular vein. Pulmonary arterial (PA) and systemic pressures and serial pulmonary angiograms (used to evaluate regional blood flow) were obtained immediately after embolization and hourly up to six hours after embolization. Selected dogs were studied at intervals to seven days. In all dogs, pulmonary embolization was recognizable by an increase in mean PA pressure (4 to 25 mm Hg), dilatation of the main pulmonary arteries, and by readily observable abnormalities on the pulmonary angiograms, but no evidence of pulmonary vasoconstriction was observed. In 19 of 22 dogs, mean PA pressure and PA size closely approximated normal by four hours. Serial angiograms revealed some striking improvements in regional blood flow. Blood flow in many vessels initially obstructed was normal in four hours. In some dogs, angiographic evidence of embolization at four hours was slight and detectable only by comparison with control angiograms. However, serial plain chest X-rays of dogs embolized with radiopaque blood clot indicated that the emboli were still present. Disappearance of evidence of vascular blockage despite the continued presence of clots in the pulmonary vasculature was attributed to either partial lysis or retraction or molding of the clots.

Vascular Resistance in the Large Pulmonary Arteries in Infancy (P)

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A decrease in pulmonary resistance following birth has been described in animals and in man. This decrease, rapid after birth and more gradual over the next weeks, has been ascribed to the opening of the pulmonary vascular bed, followed by the regression of pulmonary arterial musculature. We wish to present another mechanism for the increased pulmonary resistance noted during the neonatal period and describe an entity of "physiological" bilateral peripheral pulmonic stenosis.

Approximately 25 infants under four months of age have been found at catheterization to have a pressure gradient from main to peripheral pulmonary artery. In six of these infants, this was the only finding; in the remainder, associated lesions were present. In five cases with associated lesions (patent ductus arteriosus, ventricular septal defect), recatheterization 2 to 20 months later revealed no gradient. It was therefore thought that this represented a temporary physiological phenomenon. On cineangiograms, the main pulmonary artery of these children with the gradient was large and domelike in configuration. The peripheral pulmonary arteries arose from this vessel at a fairly acute angle and were significantly smaller in caliber, although there was no obvious area of stenosis. With growth of the peripheral arteries, the angle of origin becomes less and the disparity in size between the main and peripheral arteries decreases. In calculation of pulmonary resistance, a difference of as much as 2 units/m^2 was seen when main pulmonary arterial pressure and peripheral pulmonary arterial pressure were used and compared.

Direct Effects of O_2, CO_2, Nucleotides, and Ischemia on Coronary Resistance and Ventricular Force in the Intact Heart

Robert M. Daugherty, Jr., Jerry B. Scott, Joe M. Dabney, Booker T. Swindall, and Francis J. Haddy, Oklahoma City, Oklahoma

In previous studies, reduction of coronary blood flow decreased ventricular contractile force and coronary resistance and increased the vasodilator activity of coronary sinus blood. Elevation of coronary flow did the reverse. These observations suggested that force and resistance are, in part, flow-regulated through changes in the concentration of oxygen and/or metabolites. In this study, the local effects on force and resistance of oxygen and some of the proposed metabolites were examined. In 11 dogs, femoral arterial blood was passed through an isolated lung and perfused at a constant rate (123 ml/min) into the left common coronary artery. Coronary perfusion pressure (P), left ventricular contractile force (F), and pO_2 and pH of the perfusing blood were measured: (1) during ventilation of the isolated lung with various O_2-CO_2-N_2 mixtures; (2) during intracoronary injection of 20 μg adenosine and ATP; and (3) following a 30-second period of interrupted flow ("ischemia"). In six dogs, femoral venous blood (106 ml/min) was used as the perfusate.

Reduction of pO_2 from 92 to 30 mm Hg (pH constant at 7.64) decreased P 12% and did not affect F. Elevation of CO_2 (pH falling from 7.65 to 7.23 and pO_2 rising from 89 to 107) decreased P 15% and F 30%. Adenosine and ATP reduced P 24% and 30%, respectively, but did not affect F. "Ischemia" decreased both P and F by 34%. Reduction of pO_2 from 105 to 9 (O_2 content falling from 15.7 to 0.4 vol% and pH rising from 7.38 to 7.42) decreased P 48% and F 30%. Reduction of CO_2 (pH rising from 7.38 to 7.92 and pO_2 falling from 107 to 100) increased F 29%, but did not regularly affect P.

These observations suggest that the effects of small to moderate changes in flow on resistance and force might be explained by a combination of changes in the concentrations of CO_2 and nucleotides. The effects of "ischemia" might be explained in the same way and/or by a large change in the concentration of O_2. Other studies suggest that O_2 may be effective via metabolites.

Fluorescein Photography in Obstructions of the Retinal Arterial Supply

Noble J. David, Edward W. D. Norton, J. Donald Gass, and Robert R. Sexton, Miami, Florida

A study has been made of rapid-sequence fluorescein photographs of the fundus oculi in control subjects and in patients with obstructions to the retinal arterial supply with the Zeiss fundus camera equipped with appropriate color filters and a custom-built power supply allowing serial photography at a maximum rate of one per second.

Two patients with internal carotid arterial occlusion and profoundly lowered retinal arterial pressures by ophthalmodynamometry demonstrated a delayed arterial appearance of the dye and a further delay in the onset and development of the pattern of venous filling as compared with circulatory events in the opposite eye.

In three patients with central retinal arterial occlusions, pronounced but variable delay in both arterial and venous filling of different sectors of the retina were observed. In one patient, the macular retinal circulation, apparently fed by a proximal

branch of the central artery or a cilioretinal artery, made its circuit seven seconds before circulation through the remaining fundal vessels was observed.

Obstructions within the retinal arteriolar branches caused "streaming" and greatly delayed filling into the capillary bed and venous collection system in the area irrigated by the compromised arteriole, even when retinal tissue seemed to be undamaged. One such eye demonstrated an irregularly dilated quadrantic vein, typical of the so-called "venous-stasis retinopathy," supplied by an artery almost totally occluded by a highly refractile plaque. Tardy filling of this vein was noted, as well as retention of fluorescent blood long after the other retinal veins had emptied.

Fluorescein retinal angiography permits direct observation of the retinal vascular dynamics presently unattainable by other means.

Effect of Aortic Clearance on Measurement of Left Ventricular Volume by Thermodilution

Paul R. David, Thomas J. Knopp, and H. J. C. Swan, Rochester, Minnesota

Washout curves were recorded from the ascending aorta (AA) or the outflow tract of the left ventricle (LV) in ten anesthetized dogs after diastolic injection of 2 to 4 ml of cool saline or indocyanine-green into the AA or LV. The thermistor catheters (time constant, 0.1 second) were placed via the arterial system. An injecting catheter was introduced into the LV by transseptal puncture.

In 250 injections into the aortic root with sampling from the AA, no curve showed a complete disappearance of the indicator with the first systole. All showed that blood ejected from the LV mixed with the aortic contents. Thus, indicator cleared in an exponential fashion, with a mean residual fraction (K) of 0.46 (range, 0.15 to 0.75). Larger K values appeared to be associated with small stroke volumes.

K values for LVO (left ventricular outflow) after LV injection were smaller than the corresponding KAA values for sampling. Combination of the two K values (injection, aortic root and sampling, AA; and injection, LV and sampling, LVO) as a convolution of exponentials resulted in a value which approximated K (injection, LV; sampling, AA).

These data indicate that the AA acts as a mixing chamber (volume and mixing characteristics undefined and probably inconstant). It is suggested that an assumption basic to the determination of ventricular volume by upstream sampling (concentration [C] aorta $= C_{LV}$ for the immediately preceding beat) is seriously violated. A two-compartment washout system may be the more correct model.

Double-Inlet Left Ventricle: Report of Two Cases with Embryological Considerations (P)

Ma. Victoria de la Cruz and B. Lynn Miller, Mexico City, Mexico

Two cases are presented in which both atria empty completely or partially into the left ventricle, this condition being called *double-inlet left ventricle*. Consideration is given to the embryological implications of this occurrence.

Both cases occurred in situs solitus individuals; that is, the atria were normally situated. There was a transposition of the great arteries in each. In one case the ventricles were normally situated, and in the other there was ventricular inversion, with the morphologically left ventricle situated to the right and the morphologically right ventricle on the left. The atrioventricular valve rings were separate and the leaflet tissue complete and without clefting in both cases. In both, the left atrium opened into the left ventricle. The right atrium opened entirely into the left ventricle in one case, and in the other overrode the ventricular septum, but with its major portion opening into the left ventricle.

The importance of the condition of double-inlet left ventricle is the demonstration that both atria are connected to the morphologically left ventricle, whether situated to the left or to the right. This recalls a stage of development of the heart in the embryos of various species and lends strong support to the theory that in humans, too, both atria initially connect with the left ventricle and by expansion the right atrium comes to connect with the right ventricle. One would speculate that there was a teratogenic agent, possibly viral, acting in these cases, at approximately four weeks ovulation age, to cause the arrest in development resulting in double-inlet left ventricle.

Hemodilution with Fresh-Frozen Plasma in a High-Flow System: Studies of Oxygen Transport, Acid-Base Balance, and Hemodynamics in Sixty Patients

Dominic A. DeLaurentis, William L. Winters, Jr., Lyndall Molthan, and Julio C. Davila, Philadelphia, Pennsylvania

Cardiopulmonary bypass using fresh-frozen plasma as a diluent was performed in 60 patients. Dilution was gradually increased from 14 ml/kg to 55 ml/kg. Currently, plasma constitutes 50 to 75% of the prime. In group I the average esophageal temperature was 35 C, and in group II the average was 31 C.

Perfusion time averaged 71 minutes in group I and 109 minutes in group II. Perfusate uptake averaged 12.5 ml/kg in group I, and 26 ml/kg in group II. Net hemolysis averaged 45 mg %/hr

in both groups. Blood volumes before and after bypass were similar, and averaged 83 ml/kg before and 74 ml/kg after bypass. Hematocrit average decreased from 43% to 39%.

Arterial oxygen saturation averaged 98% in both groups. The arteriovenous saturation differences averaged 25%. In group I the oxygen uptake preperfusion averaged 93 ml/min/m^2, 133 ml/min/m^2 during perfusion, and 114 ml/min/m^2 postperfusion. In group II the oxygen uptake averaged 93, 77, and 104 ml/min/m^2 during the same periods.

Immediately postperfusion, pH averaged 7.52, with a range of 7.32 to 7.72. Bicarbonate concentration at this time averaged 22.4 mEq/L in group I, and 24.3 mEq/L in group II. Carbonic acid concentration averaged 1.2 mM/L in both groups. Postperfusion sodium and potassium levels were normal.

The over-all mortality rate was 25%. Approximately 70% of the patients had single or multiple valve replacement. No deaths could be directly attributed to the perfusion. This natural diluent seems superior to electrolyte solutions in prolonged perfusion.

Pulmonary Hemodynamic Effects of Amyl Nitrite in Normal Man

Antonio C. de Leon, Jr., and Joseph K. Perloff, Washington, District of Columbia

Amyl nitrite is an important pharmacological agent in the auscultatory, phonocardiographic, and physiological assessment of heart disease. Although the drug's systemic hemodynamic effects have recently been investigated, little data are available on the *pulmonary* circulatory effects. Accordingly, observations were made on 18 normal subjects aged 20 to 32 years. While brachial arterial (BA), pulmonary arterial (PA), and right ventricular (RV) pressures were recorded, dye-dilution outputs were performed before and at the height of systemic nitrite effect.

Reflex tachycardia (+50%, $P < 0.001$) initiated a 68% rise in cardiac index ($P < 0.001$) and a 28% decline in mean recirculation time ($P < 0.001$). BA mean pressure declined 36% ($P < 0.001$), while PA mean rose 20% ($P < 0.001$), implying a significant increase in venous return. Pulmonary resistance (PVR) fell 29% ($P < 0.01$), while systemic resistance (SVR) fell 54% ($P < 0.001$). RV minute and stroke work increased, respectively, by 99% ($P < 0.001$) and 31% ($P < 0.01$), whereas LV minute work remained unchanged (+12%, $P < 0.5$) and LV stroke work declined 23% ($P < 0.01$). RV end-diastolic pressure decreased 30% ($P < 0.01$), with no significant change in right atrial mean (−7%, $P < 0.5$).

Amyl nitrite inhalation in normal man appears to cause a more profound fall in SVR than in PVR. Thus, augmented flow through the two circulatory beds is met with a *decrease* in *systemic* mean arterial pressure and *LV* stroke work, but with a *rise* in *PA* mean pressure and *RV* stroke work. Clarification of these hemodynamic effects should enhance the usefulness of amyl nitrite as a clinical and physiological diagnostic agent.

Studies with Tritiated Digoxin in Anephric Human Subjects (P)

James E. Doherty and William J. Flanigan, Little Rock, Arkansas

Digoxin is excreted primarily by the kidney as the unchanged glycoside, 70 to 80% of the total dose being recovered from the urine in a seven-day study. The purpose of this study was to discover if an alternate excretion mechanism was present in patients rendered anephric prior to renal transplant. Five anephric patients were given 1.0 mg tritiated digoxin intravenously. Frequent blood specimens were obtained and all stools were collected for seven days. Peritoneal dialysis was usually performed late during the study and samples of dialysate were saved. Digoxin was extracted from all specimens with chloroform, passed through an alumina column, eluted with a chloroform-ethanol mixture, evaporated, counting solution added, and counted in a liquid scintillation counter. This method will extract 96% of digoxin or its metabolites. Recovery of tritiated digoxin from the stool was increased to 31% of the total dose administered, compared with 12% in patients with normal renal function. Small amounts of digoxin were recovered in the dialysate: 0.6 to 1.7% of the total dose. Serum digoxin levels were elevated and serum half-time increased to approximately three times the normal value of 33 hours. It is apparent that the liver assumes a larger role in the excretion of digoxin in anephric individuals. One-third of the usual maintenance dose should suffice to maintain digitalization in anephric or severely oliguric patients.

Tissue Turnover and Concentration of Tritiated Digoxin in Dogs

James E. Doherty and William H. Perkins, Little Rock, Arkansas

Selective tissue distribution of digoxin has been demonstrated in the human, the greatest quantities being present in heart, kidney, and liver, respectively. Serum levels are much lower than tissue levels. In a seven-day study, the mean serum half-time ($T_{½}$) is 33 hours after an intravenous dose of digoxin, and 80 to 90% of digoxin can be recovered from the urine and stool of patients

with congestive heart failure. This study was performed to determine if the release of digoxin from tissue was as selective as its deposition in the tissue, or whether the concentration in various tissues shows a fall proportional with the serum T½.

Thirty-four dogs were given 0.5 mg tritiated digoxin intravenously and sacrificed from 30 minutes to 48 hours later. Frequent serum specimens were collected. Autopsies were done and specimens of adrenal, bladder, brain, colon, diaphragm, heart, kidney. liver, lung, ovary or testis, pancreas, skeletal muscle, small intestine, spleen, and uterus were obtained. Digoxin was extracted with chloroform from all specimens, passed through an alumina column, eluted with a chloroform-ethanol mixture, evaporated, and counting solution added. Counting was done with a liquid scintillation counter.

The data reveal that the composite T½ for serum was 23 hours; heart, 26 hours; kidney, 22 hours; and for liver, 23 hours. The heart:serum ratio was 58:1 at 12 hours. A blood-brain barrier for digoxin was demonstrated. The serum T½ thus reflects the release of digoxin from all tissues, particularly heart muscle, despite initial selective distribution.

Effect of Digitalis in Compensated and Decompensated Patients with Internal Cardiac Pacemakers (P)

Ephraim Donoso, William G. Stein, Leonard Schloff, Lawrence J. Cohn, and Charles K. Friedberg, New York, New York

Seven patients with fixed-rate internal electrical pacemakers for treatment of complete heart block were studied to determine the effect of digitalis in the presence of cardiac decompensation. Arterial pressures and cardiac outputs by dye dilution were determined before and after rapid digitalization with intravenous ouabain (0.01 mg/kg). All subjects were studied while they were at rest in the supine position; six were also studied during exercise on a bicycle ergometer.

Four patients with overt or borderline cardiac decompensation had a subnormal cardiac index (CI) at rest (average, 2.3 L/min) which did not increase significantly during exercise in the three patients who were exercised (average, 2.4 L/min). Following digitalization, the resting CI increased significantly (average, 2.7 L/min) and rose further in the three patients who had exercise studies (average, 3.7 L/min).

The remaining three patients were in cardiac compensation. In two, the resting CI was subnormal (average, 2.4 L/min) and increased significantly during exercise (average, 3.2 L/min). Following digitalization, there was no significant change in the CI at rest (average, 2.4 L/min) or during exercise (average, 3.5 m/min). After digitalization, the CI fell to a subnormal level (2.3 L/min) and rose during exercise to the predigitalis level (3.3 L/min).

It appears that digitalis is an effective inotropic drug in decompensated patients who are paced electrically. In the absence of decompensation, there is either no effect or an unexplained decrease.

Transluminal Catheter Treatment of Arteriosclerotic Obstruction (P)

Charles T. Dotter, Melvin P. Judkins, and Louis H. Frische, Portland, Oregon

Since January, 1964, a method based upon arterial catheterization techniques has been used in the treatment of over 70 arteriosclerotic obstructions, with good results in 60%. Although the method has been successfully applied to iliac, subclavian, and coronary arterial lesions, most of the procedures in this series were done for arteriosclerotic obstructions of the femoropopliteal system.

The transluminal recanalization technique was used originally as an alternative to amputation for arteriosclerotic gangrene. Its early success in averting scheduled amputations led subsequently to a wider selection of cases, including many who were formerly considered candidates for surgical reconstruction or bypass grafting. The favorable results support our growing conviction that this technique may in time become the treatment of choice for most peripheral arteriosclerotic vascular obstructions.

Briefly, transluminal recanalization is performed by passing a guide through the narrowed or obstructed arterial segment. Dilating catheters are then advanced over the guide, producing smooth luminal dilatation rather than reaming or removal of the previously obstructing atheromatous material. High-quality fluoroscopy is essential; intermittent injections of heparin, angiographic contrast agents, gaseous CO_2, and specially designed probes are important aids. Local or spinal anesthesia suffices. Procedure time ranges from ten minutes to over two hours. In our experience, mural perforation, atheromatous embolization, and reclosure have not been important problems.

Future widespread application by others, using both percutaneous and direct surgical approaches, should hasten refinement of instruments and extend applicability of this technique to other sites of disease, especially in the renal, carotid, and coronary arteries.

Influences of Hypoxemia and Acidemia on Ventricular Function in the Newborn Lamb (P)

S. Evans Downing, Norman S. Talner, and Thomas H. Gardner, New Haven, Connecticut

Varying degrees of acidemia and hypoxemia are experienced by normal and asphyxiated infants at birth. Nevertheless, the influences of these metabolic alterations on cardiac function in the newborn have not been systematically examined. The performance of the left ventricle was studied in lambs one to four days old, utilizing a preparation which permitted control and measurement of aortic pressure, cardiac output, heart rate, and temperature. Arterial pH, pO_2 and pCO_2 were continuously measured with a Jewett flow-through electrode assembly. Reduction of arterial pH to 6.9 by HCl or lactic acid infusion was associated with no immediate impairment of ventricular function.

Most lambs showed no change when acidemia was maintained for periods exceeding two hours. Lowering the arterial pO_2 to 25 to 35 mm Hg by 6% to 8% oxygen ventilation caused minimal reduction of left ventricular function when pH was within the normal range. In the presence of acidemia, on the other hand, a similar reduction of pO_2 engendered a marked deterioration of cardiac function. Correction of the acidemia by $NaHCO_3$ infusion during sustained hypoxemia caused a prompt improvement of myocardial performance, indicating partial reversibility of the depression.

The reduced oxygen capacity of the blood during acidemia (Bohr shift) may reduce oxygen delivery to the myocardium, thereby producing a greater degree of myocardial hypoxia. Furthermore, intracellular pH may be reduced to a greater extent during hypoxia consequent to anaerobic metabolism than is induced by the same level of acidemia at normal oxygen tensions.

Bacterial Endocarditis in Young Patients on Antirheumatic Prophylaxis (P)

Eugenie F. Doyle, Mario Spagnuolo, Angelo Taranta, New York, New York, Ann G. Kuttner, and Milton Markowitz, Baltimore, Maryland

Fifteen patients from a population of 8,000 patient years on antirheumatic prophylaxis developed 16 episodes of bacterial endocarditis. Four were under 13 years; 11 were aged 13 to 25 years. All had rheumatic heart disease. Nine were receiving oral penicillin, four sulfadiazine, and two benzathine penicillin parenterally. The mean duration of prophylaxis was 6.4 years, but four patients had interrupted prophylaxis just before onset of endocarditis.

Blood cultures, positive in all cases, in 13 yielded α-streptococcus (only two were penicillin-resistant), in two *Staphylococcus albus* (both penicillin-resistant), and in one *Neisseria sicca* (penicillin-sensitive). All four patients with penicillin-resistant organisms were on oral penicillin. Penicillin was successfully used in all cases with penicillin-sensitive organisms. The two penicillin-resistant α-streptococcus cases responded to penicillin and other agents; one staphylococcus endocarditis responded to penicillin and streptomycin; the other ended fatally from cerebral embolism, despite heavy dosage of penicillin, oxytetracycline, and methicillin.

Unusual clinical features included joint involvement in 12 patients; seven had definite arthritis. Four patients had neurological involvement: two had hemiparesis (one died), one had meningitis, and a fourth had both. Splenomegaly was noted in only two patients; petechiae were noted in nine. These data suggest that the incidence of bacterial endocarditis in this population is low; that resistance of the organism to penicillin may be more common in patients receiving oral penicillin, but does not constitute a major therapeutic problem.

Mechanisms of Second-Degree Atrioventricular (A-V) Block

Leonard S. Dreifus and Yoshio Watanabe, Philadelphia, Pennsylvania

Besides the two commonly recognized types (Mobitz I and II) of second-degree atrioventricular (A-V) block, several other variations have been known clinically. However, mechanisms of periodicity and the precise site of transmission failure remain obscure. In order to reveal these points, representative clinical electrocardiograms showing second-degree and advanced second-degree A-V block were compared with similar records obtained in perfused, spontaneously beating rabbit hearts in which two microelectrodes were simultaneously impaled in the A-V junction.

Typical Wenckebach (Mobitz type I) periodicity was characterized by major and progressive transmission delay in the N region of the node, with failure of propagation in the NH region. Additional delay in or below the NH region often engendered atypical Wenckebach cycles with increasing increments of the P-R interval and a slowing of the ventricular rate. Contrarily, Mobitz type II block was characterized by the development of major delay and conduction failure in or below the His bundle. In other instances, concealed re-excitation of A-V nodal fibers caused sudden failure of transmission. In advanced second-degree block, the first nonconducted impulse

never penetrated deeper than the subsequent blocked beats, a contradiction to popular concepts. Inhomogeneous conduction in contiguous regions of the A-V junction was frequently observed during the development of A-V block.

Hence, the P-R and R-R intervals in the various types of second-degree block result from a complex interplay of conductivity in various regions of the A-V junction. The actual sites of transmission failure and the mechanisms involved in second-degree A-V block were observed.

Supernormal Phase of Myocardial Excitability in Man

William Dressler, Sterling Jonas, and Edward Schwartz, New York, New York

Five patients paced by an implanted pacemaker were studied after the intensity of the electrical impulses (because of break of electrode wires) had dropped to subthreshold values. The weak electrical impulses elicited responses only when they fell in close proximity to a beat of the basic ventricular rhythm. This suggested the existence of a supernormal phase of myocardial excitability. In two patients, conditions were particularly favorable for study of supernormality inasmuch as subthreshold stimuli continued to be present for several days, apparently without change. Whenever the catheter pacemaker, which controlled the basic ventricular action, was turned off responses to the subthreshold stimuli of the implanted pacemaker were abolished. When transvenous pacing was resumed, early-arriving subthreshold stimuli were effective again. By varying the rate of the basic ventricular rhythm, it was possible to determine the time of onset and the duration of the supernormal phase in relation to various lengths of the basic ventricular rhythm.

It was found that the period of supernormal excitability consisted mostly of two phases: one in which every subthreshold elicited a response, that is, a phase of high supernormality; and another phase, thought to represent low supernormality, during which some subthreshold stimuli were effective while others were not. In general, supernormal excitability began earlier with faster ventricular rates.

Of great interest were observations on the site of the supernormal phase in relation to the T wave of the preceding basic ventricular beat. In one case, the supernormal phase began at the end of T; this was in accord with observations reported by others. In the second case studied, supernormality started at or close to the nadir of T, that is, during a phase which is usually identified with the relative refractory period.

Membrane Action Potentials, Intramural Excitation, and Anatomy of a Postmortem-Perfused Human Heart with Severe Coronary Heart Disease (P)

Dirk Durrer, Rudolph Th. van Dam, Gerrit Freud, Frits L. Meijler, J. Snijder, and C. A. Wagenvoort, Amsterdam, The Netherlands

A revived human heart with complete atrioventricular block, left bundle-branch block, old, large, posteroseptal infarction, and a recent anterior infarction was perfused for five hours with a modified Tyrode solution containing washed beef erythrocytes and 1% hemoglobin. After this five-hour period, intracellular membrane action potentials of −85 mv were measured in apparently normal muscle cells. The influence of frequency on duration and form of the membrane action potential was studied. Changes in duration are caused by changes in phase two; the form of phase three remained constant.

Intramural conduction velocity in normal heart muscle was 30 cm/sec. Intramural electrodes were introduced at many places on the left ventricular wall. Large blocks of tissue surrounding the puncture canals were examined histologically by routine and histochemical staining techniques. Intramural excitation of the left ventricle occurred in a predominantly tangential direction, starting at a small zone of the anterior wall near the ventricular septum. The area of the posterior wall surrounding the scar was activated latest in the cardiac cycle.

The unipolar intramural and epicardial complexes and the bipolar complexes between consecutive intramural terminals from the scar were greatly notched. Intramural conduction in the infarction occurred by way of surviving muscle fibers.

Recent myocardial damage, as indicated by epicardial and intramural electrocardiographic abnormalities, could often be demonstrated only by histochemical techniques. In the noninfarcted parts of this hypertrophied heart, only slight interstitial edema was found with normal myocardial cells.

Electrocardiographic and Vectorcardiographic Changes in Natives of High Altitudes by Descent to Sea Level

Juan Dyer, Raul Gamboa, Dante Peñaloza, Emilio Marticorena, and Francisco Sime, Lima, Peru

Right ventricular hypertrophy and pulmonary hypertension are common observations in healthy people born and living permanently at high altitudes. Right ĀQRS deviation, increased basal QRS vectors, and clockwise rotation of the horizontal QRS loop are frequently observed in these

subjects. Thirty-eight adults and 12 children native to high altitudes were studied at 14,900 feet above sea level. Then, they were taken down to sea level where the observations were repeated periodically over two years. Hemodynamic studies were performed in 11 of these subjects at high altitude and repeated after two years of residence at sea level.

The pulmonary pressure became normal at rest after two years of residence at sea level. The right-axis deviation decreased, and the values of the ÂQRS vector became near normal in adults. The final QRS vectors diminished, while the voltage of mid-QRS vectors increased. Clockwise rotation of the horizontal QRS loop remained in some cases, and changed to "eight figure" in others. The T wave became too high in right precordial leads. The heart rate decreased significantly.

This knowledge is important, because the electrocardiographic and vectorcardiographic patterns of high altitude residents are often misinterpreted as abnormal, not only while they are living at high altitude, but also after long residence at sea level.

Patent Ductus Arteriosus at High Altitudes: Clinical Studies

Juan Dyer, Fernando A. Tapia, Dante Peñaloza, Nestor Gonzales, and César Vasquez, Lima, Peru

At high altitudes, chronic hypoxia produces structural changes in the pulmonary vasculature, moderate pulmonary hypertension, and right ventricular hypertrophy. These changes may alter the clinical picture and the natural history of the ductus arteriosus (PDA) in that environment. The clinical study of PDA at high altitude is justified, because its incidence is more frequent than at sea level.

Clinical, roentgenologic, and electro-vectorcardiographic observations were made in 100 natives with PDA from altitudes over 9,840 feet above sea level, their ages varying from 8 months to 29 years. The diagnosis was confirmed by surgery or cardiac catheterization. These observations were compared with a large series of patients from sea level with PDA.

Several differential features were observed in patients with PDA at high altitudes. There was a higher incidence of cyanosis and exercise intolerance; the typical "machinery-like" murmur was not found in 37 of the cases—of these, 20 had only a systolic murmur, 15 a systolic-diastolic murmur, and 2 had no murmur. Abnormal electrocardiograms with right-axis deviation and pure right or combined ventricular hypertrophy were found in most cases, in contrast with normal electrocardiograms or a pure left ventricular hypertrophy pattern found in patients from sea level. Roentgenologic evidence of significant cardiac enlargement, combined ventricular hypertrophy, and prominent dilatation of the pulmonary artery were almost constant findings. These observations may be explained by the presence of a more severe degree of pulmonary hypertension found in PDA at high altitudes.

Perforation of the Right Ventricle: A Complication of Transvenous Endocardial Catheter Pacemaking

Alphonse C. Edmundowicz, David Z. Morgan, and Robert J. Marshall, Morgantown, West Virginia

The use of surgically implanted pacemakers in the management of complete heart block has gained wide acceptance. Interim transvenous endocardial pacemaking prior to surgery has many advantages. It replaces an emergency thoracotomy in these often elderly patients with a semi-elective procedure. Ventricular stabilization prevents Stokes-Adams attacks and permits time for improvement in cardiopulmonary and renal function and for treating infections. The risks of anesthetic induction and surgery are reduced. Prolonged endocardial pacemaking, however, is not without hazard. We have experienced three instances of right ventricular perforation, subsequently confirmed at operation, among 20 patients paced with a conventional bipolar catheter for from two to seven days prior to surgery. This complication should be suspected when the heart suddenly fails to respond to the pacemaker, or the patient complains of shoulder pain. Confirmation is readily obtained by lateral X-ray films. Subsequently, we have used modified bipolar catheters with electrodes (1-cm apart) located 5 cm proximal to the catheter tip. With the catheter tip positioned in the main pulmonary artery, the right ventricular outflow tract is stimulated; this permits stable pacemaking while minimizing the risk of ventricular perforation.

Hemodynamic and Catecholamine Changes During Exercise in Patients with Chronic Obstructive Pulmonary Disease

Robert H. Eich, Richard P. Cuddy, Udomporn Kashemsant, Syracuse, New York, William A. Vincent, Evansville, Indiana, and Harold Smulyan, Syracuse, New York

The relationship between hemodynamics and circulating catecholamines was studied in 27 patients with chronic obstructive pulmonary disease. The clinical diagnosis was confirmed with pulmonary function studies, and none of the patients

was in congestive heart failure. The patients were studied by right-heart catheterization. Cardiac output (CO) was measured by the indicator-dilution technique, and catecholamines by the trihydroxyindole method. The mean resting values were: CO, 5.47 L/min; pulmonary artery pressure (PAP), 40/19, mean 26 mm Hg; pulmonary capillary pressure, 11 mm Hg; arterial norepinephrine (NE), 0.62; and pulmonary artery NE, 0.51 μg/L plasma. Epinephrine was rarely found. No relationship was found between the NE level and PAP. Anoxia, using 16% inhaled oxygen, lowered arterial saturation to 72%, but did not alter the catecholamines. Supine leg exercise for three minutes increased the CO 1.74 L/min, PAP 16/8, arterial NE 0.33, and pulmonary artery NE 0.74 μg/L. Intravenous NE infusion to increase the NE levels to those found with exercise lowered the CO and PAP. Blocking the effect of circulating norepinephrine by infusing phentolamine (5 mg initially and 1 mg/min for three minutes prior to and during the exercise) modified the exercise response in two subjects. Cardiac output increased to the same or higher levels with a lower pulmonary and systemic vascular resistance. With exercise, in patients with obstructive pulmonary disease, the rise in norepinephrine appears to be sufficient to significantly affect the exercise response.

Blood Viscosity and Fibrinogen Following Cerebral Infarction (P)

Seymour Eisenberg, Dallas, Texas

There are various hypotheses concerning the circumstances leading to complete occlusion of the diseased cerebral blood vessel; prominent among these is the concept that alterations in the fluid character and coagulability of the blood initiate this final thrombotic event. This study was undertaken to examine the role of alterations in blood viscosity in cerebral vascular thrombogenesis. Fifty subjects with recent (< 24 hours) cerebral infarction were studied. Fibrinogen concentration and blood viscosity (cone plate) were determined repeatedly. Subjects with obvious dehydration or infection were excluded.

1. Blood viscosity was significantly increased, particularly at slower shear rates (12 sec–1). There was a 28% increase in viscosity, and all but three values exceeded the normal mean.

2. The mean hematocrit value for these subjects (46 mm) was only slightly increased over normal.

3. Fibrinogen concentration was consistently elevated; the mean value was 550 mg per 100 ml.

4. Acute myocardial infarction occurred in three subjects with elevated blood viscosity and fibrinogen values.

These observations made after the thrombotic event may not reflect circumstances initiating that event. Cerebral infarction, by inapparent mechanisms, may stimulate this hyperfibrinogenemic viscosity response which, in turn, may result in a thrombotic diathesis. The changes are more consistent and of greater magnitude than those encountered in this laboratory following acute myocardial infarction. The viscosity changes in these subjects with "strokes" apparently were unrelated to hemoconcentration, inasmuch as the hematocrit values were only slightly elevated. This contrasts with the circumstances following treatment in cardiac decompensation, where selective loss of plasma volume invokes erythremia, hyperfibrinogenemia, and increased viscosity.

Beta-Adrenergic Receptor Blockade and Plasma Catecholamine Determination as Aids in the Analysis of the Origins of the Hemodynamic Responses to Link Trainer Simulated Flight (P)

Harald Eliasch, Anders Rosén, Stockholm, Sweden, and Hugh M. Scott, Montreal, Quebec, Canada

Link trainer simulated flight provides a meaningful model for the study of upright cardiovascular adjustments during stressful situations in man. Hemodynamic and fluorimetrically determined arterial plasma catecholamine concentrations were measured in 11 pilots during two consecutive rest and simulated flight periods. The second "flight" elicited mean hemodynamic responses similar to the first in four untreated subjects, but significantly different responses in the remaining seven, in whom beta-adrenergic receptor blockade (β-B) was induced with 5 mg of propranolol administered intravenously between the periods.

Dye-dilution–determined cardiac output (L/min) increased a mean of 55% during the initial flights, while after β-B, a lower resting level preceded a minimal rise during flight (before β-B: rest 5.74 ± 0.55, flight 8.87 ± 1.21; after β-B: rest 4.35 ± 0.50, flight 4.86 ± 0.52). Both heart rate and stroke volume underwent similar modifications. Estimated total peripheral resistance (arbitrary units) rose markedly at rest after β-B (to 2.89 ± 0.26), and was not influenced by the second flight, contrasting with a mean 20% decrease during the first flight (1.91 ± 0.18 to 1.56 ± 0.19). Despite these underlying changes, β-B did not decrease the resting arterial pressure modalities or the 20% higher levels that occurred during flight. Plasma norepinephrine concentration appeared elevated initially at rest (mean,

0.86 ± 0.20 μg/L), and did not change significantly thereafter. Plasma epinephrine was detected inconsistently.

Cardiac and peripheral beta-adrenergic receptor activity, not necessarily epinephrine-mediated, plays a dominant role in producing the upright cardiovascular adjustments during stressful situations. Pharmacological blockade of this activity does minimize the tachycardia and flow responses, but not the blood pressure increases that occur in such situations; it is therefore likely to provide only partial protection from their threat of increased heart work to any already compromised myocardium.

Serum Protein Abnormalities in Myocardial Necrosis

Robert S. Eliot, Murray A. Gibas, and Hiroshi Mizukami, Minneapolis, Minnesota

Among 26 patients experiencing different forms of myocardial necrosis, disc electrophoresis with benzidine staining demonstrated certain serum protein abnormalities. The abnormalities appear most prominent with benzidine staining and did not appear as well with Amido-Schwartz staining techniques. Patients studied include all recent admissions to the hospital for suspected acute myocardial infarction, patients with electrical cardioversion, selected patients with liver, thyroid, and other diseases, and patients with crush injury.

Serum electrophoretic abnormalities were observed among 11 of 12 patients thought to have had myocardial infarction within 6 to 12 months, one of two patients with percutaneous left ventricular puncture, both patients with d-c cardioversion, and one of ten patients with liver, thyroid, or other disease. Those patients with crush injury demonstrated free serum myoglobin and hemoglobin, but failed to show the abnormality demonstrated in the aforementioned conditions. Of 12 normal subjects studied, none showed the aforementioned abnormalities.

The serum abnormality does not appear to be related to skeletal muscle injury or to liver disease; instead, when present, it appears to indicate not only myocardial necrosis of acute onset, but also of previous (up to six months) onset. This fast and simple new technique may represent an additional parameter for clinical study of patients suspected of having myocardial necrosis.

Inhibition of Catecholamine Synthesis in Man (P)

Karl Engelman, David Horwitz, Sidney Udenfriend, and Albert Sjoerdsma, Bethesda, Maryland

Significant inhibition of catecholamine synthesis has been achieved for the first time in man by the administration of L-alpha-methyl-para-tyrosine (α-MPT), a compound which is a potent inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis.

In two patients with benign pheochromocytomas who received up to 1,200 mg/day of α-MPT orally, catecholamine synthesis was inhibited by as much as 60%. This was shown by a decrease in urinary vanilmandelic acid (VMA) excretion from an average control value of 27 mg/day to an average treatment value of 11 mg/day. Similar studies in hypertensive patients receiving 400 to 1,200 mg/day α-MPT have also shown marked reductions in VMA excretion. It should be emphasized that the drug has thus far been given in submaximal doses, and studies are currently in progress in a number of subjects, including six more with pheochromocytoma, utilizing larger doses of α-MPT. At the dosages employed, sedative effects were observed in most of the patients, but little effect was produced on the blood pressure, except in patients with pheochromocytoma. In the latter, concomitant with the fall in VMA excretion, there was a decrease in blood pressure; VMA excretion and blood pressure rose when the drug was withdrawn.

We would predict that α-MPT or a similar compound will be useful in the chronic treatment of patients with unresectable pheochromocytoma, and may make preoperative and surgical care of patients with this condition considerably less hazardous by rendering the tumor nonfunctional. In addition to therapeutic prospects, α-MPT may afford new means for studying the role of catecholamines in various diseases.

Effects of Beta-Sympathetic Blockade on Coronary Blood Flow in Hemorrhagic Shock in Dogs (P)

Mark L. Entman, Arthur M. Martin, Jr., Eileen M. Mikat, Gleb G. Bourianoff, and Donald B. Hackel, Durham, North Carolina

Coronary blood flow (CBF) in hemorrhagic shock was studied in dogs weighing 15 to 25 kg. CBF and cardiac output (CO) were measured in 15 animals by electromagnetic flowmeter before bleeding, following which the animals were bled to a mean blood pressure of 40 mm Hg over 30 minutes. Measurements were repeated, and eight animals were given a potent β-blocking agent, pronethalol, 170 mg/m^2, over a seven-minute period. After 15 minutes, flows were again measured in both the treated and untreated groups.

CBF decreased from a mean of 74 ml/100 g/min to 48 ml/100 g/min after induction of shock. The animals given pronethalol increased their CBF to 62.6, while the untreated group did not change after 15 minutes of shock (49.8).

In none of these experiments did pronethalol significantly alter CO. Systolic flow rate (ml/100 g/min of systole) decreased from 45.5 to 26.5 with shock induction and increased to 48.1 with pronethalol treatment. Diastolic flow rate (ml/100 g/min diastole) decreased from 111 to 75 with shock induction and did not change with pronethalol (75.6). There was no change in blood pressure after pronethalol treatment in shock.

These results demonstrate a change in systolic flow resistance without change in diastolic flow resistance; they emphasize the importance of the extravascular impedance to coronary blood flow in systole brought about by the inotropic response to intense sympathetic stimulation in hemorrhagic shock.

Vascular Anatomy of the Wall of the Heart and Its Alteration in Coronary Artery Disease (P)

E. Harvey Estes, Jr., Mark L. Entman, Henry B. Dixon, II, and Donald B. Hackel, Durham, North Carolina

Postmortem angiograms have been carried out on human hearts, using a barium suspension and a technique which fills arterioles of small size but does not penetrate capillaries. Microradiographs of the vascular architecture of the left ventricular wall have been made in 57 hearts. These have revealed a characteristic pattern: the large epicardial vessels send right-angle branches into the wall which subdivide into two types of vessels. Type A vessels divide and subdivide in the outer two-thirds of the myocardium; type B vessels plunge, without extensive branching, into the subendocardium, entering a large subendocardial anastomotic network of large size (50 to 500 μ).

Coronary artery disease is characterized by overgrowth of fine branches from type A vessels in areas of scattered fibrosis and enlargement of the subendocardial anastomotic plexus around and beneath areas of scarring.

These observations show that: (1) the myocardial vasculature is more highly organized than previously suspected; (2) a potential anastomotic network is constantly present in normal and abnormal hearts of all ages; and (3) this network is enlarged in ischemic areas in coronary artery disease.

The vessels supplying the subendocardial anastomotic plexus traverse the entire thickness of the myocardium in a manner which would permit myocardial counterpressure to exert a major influence on anastomotic flow. It is suggested that this, in addition to coronary perfusion pressure, may influence anastomotic flow into ischemic areas in coronary artery disease, explaining the fluctuations in the severity of clinical symptoms and the occurrence of clinical "attacks" in the absence of new occlusion.

Left Parasternal Pulsations in Patients with Mitral Insufficiency

Gordon A. Ewy, Lucy Gomez, and Frank I. Marcus, Washington, District of Columbia

The chest wall pulsations in the left parasternal area have been evaluated in 27 patients with mitral insufficiency. The aim of the study was twofold: first, to determine the cause of the parasternal impulse that is frequently palpable in patients with moderate to severe mitral insufficiency; and second, to compare the impulse in patients with and without concomitant right ventricular hypertrophy.

With a simple recording device, the heart and chest wall motions in the left parasternal area were recorded in relation to a fixed point in space. The recordings of all the patients revealed an impulse early in systole, and 20 of the 27 patients had a second impulse that occurred late in systole. The early systolic impulse coincides with isometric contraction of the right ventricle, as determined by the right apexcardiogram. The late systolic impulse, which peaks near the second heart sound, coincides with the peak of the regurgitant v wave in the left atrium, as determined by cardiac catheterization.

In patients with mitral insufficiency but without associated right ventricular hypertrophy, the early systolic impulse was fleeting and nonsustained. However, with increasing right ventricular pressures, the early systolic impulse became more prominent and sustained. If close attention is given to detail, these events may be appreciated at the bedside.

Discontinuation of Antistreptococcal Prophylaxis in Rheumatic Patients Free of Heart Disease: A Double-Blind Study (P)

Alvan R. Feinstein, New Haven, Connecticut, Mario Spagnuolo, Saran Jonas, Muriel Levitt, and Esther Tursky, New York, New York

Antistreptococcal prophylaxis has been discontinued in selected older adolescents and young adults without heart disease who had remained free of recurrent attacks of rheumatic fever for three to five years after an unequivocal episode. The 161 patients, of median age 17 years (range, 14 to 24 years), were randomly allocated into two groups comparable in age and in remoteness from the most recent rheumatic attack. For daily prophylaxis, one group received oral penicillin G, 200,000 units, and the other received a placebo. A double-blind procedure was used throughout the study. Patients were examined at bimonthly intervals for two and one-third years. Streptococcal infections were identified with throat-culture and antibody techniques.

In 138 patient years of observation, the oral-penicillin group developed 30 streptococcal infections (attack rate: 22 per 100 patient years) and one rheumatic recurrence (attack rate: 0.7%). In 140 patient years of observation, the placebo group developed 30 streptococcal infections (attack rate: 21%) and two rheumatic recurrences (attack rate: 1.4%). None of the attack-rate differences was statistically significant. No permanent new cardiac damage appeared in the three patients who developed rheumatic recurrences.

These results suggest that a cautious discontinuation of prophylaxis may safely be attempted in selected patients without rheumatic heart disease. Further studies are necessary to determine whether oral-penicillin prophylaxis, although apparently no more effective than placebo for preventing streptococcal infections in this age group, is superior in preventing acquired infections from progressing to rheumatic recurrences.

Morphology of the Conduction System in Ventricular Septal Defect and Tetralogy of Fallot: Correlations with the Electrocardiogram (P)

Robert H. Feldt, James W. DuShane, and Jack L. Titus, Rochester, Minnesota

Occasionally, ventricular septal defect (VSD) and tetralogy of Fallot are associated with electrocardiographic patterns similar to those usually seen with atrioventricular (A-V) canal defects. To compare the morphology of the conduction system in such examples with the morphology in examples of both anomalies associated with ECG patterns more representative for these defects, the A-V conduction system was studied by serial histological section techniques in eight hearts. In two examples of each anomaly, the ECG findings were typical of A-V canal; and in two examples of each, the ECG patterns were more representative for that anomaly and served as "controls."

In the examples of tetralogy of Fallot, the two associated with A-V canal ECG patterns differed from their controls in that fibers destined to become right bundle branch took an elongated and circuitous course. The two VSD examples with an A-V canal ECG also differed from their controls in that the origin of the right bundle was at a relatively greater distance from the A-V node.

The observations for both anomalies are similar in that the unusual ECG pattern was associated with a morphological situation which could allow for relatively early impulse conduction to the left bundle-branch system. Thus, an electrophysiological-morphological correlation compatible with current theories concerning the cause of the anomalous ECG pattern in A-V canal defects was obtained from the study of two defects distinctly unrelated morphologically to A-V canal.

Beta-Adrenergic Blockade with Propranolol in Atrial Arrhythmias

Thomas J. Fiene, John R. Griffin, and Donald C. Harrison, Palo Alto, California

Since the ventricular rate in atrial arrhythmias may be related to the influence of the sympathetic nervous system on the refractory period of the atrioventricular (A-V) node, studies were undertaken to determine the effect of β-adrenergic blockade with propranolol on ventricular rate in patients with atrial arrhythmias. Propranolol, 100 μg/kg, was given intravenously over a 10- to 30-minute period with continuous electrocardiographic monitoring. On 17 occasions in 11 patients with atrial fibrillation, the ventricular rate slowed from an average of 98/min to 72/min. In each of five patients with atrial flutter, the ventricular rate slowed with no change in atrial rate. Both atrial and ventricular rates slowed from an average of 183/min to 117/min in four patients with atrial tachycardia and in one with nodal tachycardia.

In six patients with atrial fibrillation, the administration of propranolol diminished the increase in heart rate produced by a 15-minute infusion of the specific β-adrenergic stimulator, isoproterenol, from 64/min to 13/min. The increase in heart rate produced by treadmill exercise in six patients with atrial fibrillation was only slightly diminished by propranolol, although all started with lower resting heart rates. Heart-rate slowing occurred immediately following propranolol, persisted four to six hours, and was produced in several patients in whom digitalis had not controlled the ventricular rate.

These studies suggest that the β-adrenergic blocking action of propranolol produces a decrease in heart rate by increasing the A-V block in patients with atrial fibrillation and flutter, and by other mechanisms in atrial and nodal tachycardia.

Plasma Renin in Renal Parenchymal Hypertension (P)

Annette E. Fitz, Walter M. Kirkendall, and Mark L. Armstrong, Iowa City, Iowa

Plasma renin levels were measured in 22 patients with renal parenchymal hypertension (HT) and compared with levels found in 20 normal subjects. Peripheral venous blood was assayed by Helmer's technique, and renin activity per ml of plasma was expressed as nanograms (ng) of angiotensin amide.

Normal ambulant men and women, aged 22 to 68 years, had renin values of 3 $\pm$ 3 ng (mean and SE)/ml plasma during unrestricted salt intake. Blood pressure (BP) averaged 124/74 mm Hg.

Patients ranged in age from 1 to 52 years, and were evenly distributed between sexes. Three groups were established by tissue diagnoses: acute glomerulonephritis, chronic glomerulonephritis, and pyelonephritis. All were edema-free when studied and were ambulant except for the group of four patients with acute glomerulonephritis. This group had normal renin levels, 5.1 ± 2 ng/ml. Concurrently, blood urea nitrogen (BUN) averaged 70 mg%, and average BP was 145/91. Eight patients with chronic glomerulonephritis had comparable renin levels, 2.5 ± 1 ng/ml, with an average BUN of 57 and average BP of 158/102. In the group with pyelonephritis (ten patients), the mean renin level was higher than normal, 20 ± 9.6 ng/ml ($P < 0.02$), with average BUN 31 and average BP 172/114. The high mean plasma renin in this group was entirely due to three patients who had accelerated HT with grade III eyeground changes and thus had an additional cause for high levels. The renin values in the remaining seven patients with pyelonephritis averaged only 4 ± 2 ng/ml. The results indicate that plasma renin is ordinarily within normal limits in the major types of renal parenchymal hypertension.

Quantitation of Left-to-Right Shunts with Selective Radiocardiography

John T. Flaherty, Page A. W. Anderson, Ramon V. Canent, Jr., Madison S. Spach, and Aaron R. Levin, Durham, North Carolina

The technique of externally recording radioisotope dilution curves for left-to-right shunt detection without blood sampling can provide a major advance in cardiac catheterization if the externally recorded curves could be utilized to quantitate the shunt. This study was undertaken to develop a method for quantitating left-to-right shunts from externally recorded radioisotope dilution curves and to compare their reliability with the Fick method.

Sixty children who showed pure left-to-right shunts were studied during preoperative cardiac catheterization. Thirty children without shunts or valvular insufficiency served as controls. Lung curves were recorded with a collimated scintillation detector placed over the right lung at the anterior axillary line. Injections of 15 to 50 μc of I^{131}–sodium hippurate were made into the proximal portion of the right pulmonary artery. Blood samples were then rapidly obtained for calculations of the shunts by the Fick method.

A method of analysis was developed by dividing the curves into two major areas. The entire area of the curve below the extrapolated exponential slope from its initial peak was compared with the area between the extrapolated exponential slope and the original curve. The ratio of the areas calculated from the radioisotope curves was compared with the percentage left-to-right shunt determined by the Fick method. A correlation coefficient of 0.8814 between the radioisotope curve and Fick values was obtained for the entire group. There was separation of the ratios according to individual shunts (atrial septal defect, ventricular septal defect, and patent ductus). The regression line for each individual defect was significantly different. By knowing the level of the shunt, a comparison of values yielded an improved correlation coefficient (0.9482).

These data demonstrate that the technique of externally monitored radioisotope dilution curves of the right lung is a valid and accurate method for the detection and quantitation of left-to-right shunts, and is especially useful in small infants.

Reduction of Serum Cholesterol and Lipids by Dextran (P)

C. Thomas Flotte and Robert W. Buxton, Baltimore, Maryland

The intravenous administration of dextran (molecular weight, 70,000) to experimental animals and to patients with hyperlipemia has caused a marked and prolonged reduction in serum cholesterol, triglycerides, lipoproteins, and total lipids.

Rabbits were made hyperlipemic by the feeding of a high-cholesterol diet and antithyroid drug. The administration of dextran caused a marked reduction in serum cholesterol and other lipids, despite the continued feeding of the hyperlipemic diet.

One hundred and ninety patients with cholesterol levels ranging from 300 to 600 mg% were given 500 ml of 6% dextran daily for three days. Reduction of cholesterol was noted within 24 hours, with the maximum effect in 72 to 96 hours. After the dextran, the cholesterol ranged from 140 to 210 mg%. The lowered cholesterol levels persisted for four to five weeks, when they gradually returned to pretreatment levels. Other serum lipids were measured, and the decrease was in proportion to the reduction in cholesterol. Dextran may be an effective agent in the reduction of serum cholesterol and other lipids in patients with hyperlipemia.

Use of Ethacrynic Acid in Treatment of Refractory Edema

Walter L. Floyd, Charles E. Rackley, Durham, North Carolina, James C. Hurlburt, Winter-Park, Florida, Charles W. Harris, Denver, Colorado, and Edward S. Orgain, Durham, North Carolina

Ten edematous patients who had proved refractory to a variety of diuretic regimens were

treated with a new diuretic compound, ethacrynic acid. Edema resulted from cirrhosis in three patients, arteriosclerotic heart disease in three patients, idiopathic myocardial disease in two patients, and cor pulmonale in the remaining two patients. Treatment period varied from 15 to 30 days, and maximum dose ranged from 150 mg to 400 mg per day.

Nine patients experienced an increase in sodium and chloride excretion and diuresis of 4.1 kg to 11.2 kg in body weight. Hypochloremia occurred in all patients, and serum bicarbonate became elevated in nine patients. In spite of dietary sodium restriction, only three patients developed hyponatremia. Hypokalemia developed in eight patients and potassium supplement was necessary in seven patients. Confusion occurred during the course of therapy in six patients, and discontinuation of therapy was necessitated by confusion and/or electrolyte imbalance in six patients; resumption of therapy without untoward effect was possible in three cases. One patient died suddenly after he became confused and obtunded during a second attempt at diuresis. A second patient died of hypotension, oliguria, and rapidly progressive uremia following initial diuresis of 8 kg.

The observations indicate that ethacrynic acid may be an effective diuretic agent in otherwise refractory edema, but does possess hazardous side effects, particularly electrolyte imbalance and central nervous system dysfunction, in dosage levels above 150 to 200 mg per day.

Active Stiffness of the Intact Canine Left Ventricle

Stanley A. Forwand, Herbert J. Levine, Kevin M. McIntyre, Boston, Massachusetts, and Eliot Schechter, San Antonio, Texas

Left ventricular pressure (P), dP/dt, and aortic flow rate were recorded in 20 dogs. Knowing end-diastolic volume (thermodilution) and assuming a spherical ventricle, instantaneous radius (r), wall force ($F = \pi r^2 P$), and fiber-shortening rate (FSR = flow rate/$2r^2$) were derived. Contractile element work (CEW) was derived as force-generating work ($FGW = F_p/S$) plus fiber-shortening work ($FSW = \int F \times FSR$), where F_p = peak force and S = slope of the linear dF/dl (active stiffness)-F relation.

Two techniques were used to estimate S in the intact ventricle. In one, two consecutive systoles (1 and 2) were analyzed, differing only in a minor change in afterload, such that $CEW_1 = CEW_2$. Thus,

$$(F_p)_1/S + FSW_1 = (F_p)_2/S + FSW_2.$$

The average value for S was 17.7 ± 4.5 cm^{-1}, normalized for unit fiber length. In the second technique, two consecutive beats were analyzed: one an auxotonic control, the second an isometric contraction of the ventricle. FSR in the auxotonic beat was measured when $dF/dt = 0$ (20 to 60 msec of ejection period); dF/dt of the isometric beat was measured at the same time after the onset of pressure rise, and the ratio (dF/dt)/FSR calculated and normalized for unit length of muscle. The average S derived by this method was 17.2 ± 6.0 cm^{-1}.

Active stiffness calculated in this manner is about 60% of that reported by Sonnenblick for series elasticity of the cat papillary muscle. It is suggested that the functional active stiffness of the intact ventricle reflects not only series elasticity of muscle, but the effects of passive contractile elements and fibrous tissue (that is, valves) in series with active muscle, each of which may play an important role in disease of the human myocardium.

Corrugated Arteries: An Enigma (P)

John H. Foster, Duncan A. Killen, and Eugene C. Klatte, Nashville, Tennessee

Occasional arteriographic observation of corrugated arteries, or so-called "standing waves," has been noted by a number of authors. It has been stated that the corrugations are constant and unaffected by vasodilator drugs. On the other hand, it has been said that they are transient and found only when concentrated contrast medium is injected. Some reports have associated the corrugations with Buerger's disease; others associated the change with distal occlusion. Ten cases of corrugated arteries have been reported in the literature. In the past year, we have encountered seven patients with corrugated arteries. None have evidence of Buerger's disease. They range in age from 16 to 46 years. Three patients with corrugated arteries in the lower extremities presented with intermittent claudication, although they had normal pedal pulses. Mesenteric artery corrugations have been found on abdominal aortography in three hypertensive patients.

These patients have been restudied to determine the constancy of the corrugations and the influence of the concentration of the contrast medium, proximal arterial occlusion, sympathetic blockade, and vasodilator drugs. It is apparent that the corrugations are present on succeeding days, and even several months later; they are encountered with dilute contrast media; intra-arterial vasodilator drugs completely ablate the corrugated effect; and proximal occlusion partially ablates the change. The constancy, regularity, and symmetry of the corrugations are striking.

Corrugated arteries seem to be a relatively new entity. Their significance is as yet questionable.

Four possible etiological explanations have been developed.

Pulmonary Artery Pressure at High Rates of Pulmonary Blood Flow (P)

Noble O. Fowler and John C. Holmes, Cincinnati, Ohio

This study was made to clarify the relationship between pulmonary arterial flow and pressure, especially at high flow rates. The relationship between pulmonary arterial pressure, left atrial pressure, and pulmonary blood flow was studied in two groups of dogs. *Group 1*: In nine open-chest dogs, constant and equal systemic and pulmonary flow rates were evaluated during cardiac arrest. Pulmonary flow of 100 ml/kg/min was considered normal. Flows above 200% of normal through one lung were obtained by balloon or snare occlusion of the pulmonary artery to the other lung. *Group 2*: In four open-chest animals, pulmonary pressure/flow relationships were studied while the beating heart perfused only the left lower lobe. Adequate blood oxygenation and pH control were obtained by an artificial oxygenator.

In group 1 animals, pulmonary vascular resistance fell as the flow rate was increased from 50% of normal to 500% of normal. At 200% of normal flow, pulmonary arterial pressure ratio to control was 1.44; at 300% of normal flow, 1.83; at 400% of normal flow, 2.04; and at 500% of normal flow, the ratio was 2.32. Results were comparable in group 2. Pulmonary vascular resistance did not rise, although the rate of decrease in resistance fell with increasing flow rates.

These observations do not support the concept that the limit of pulmonary vascular distensibility is reached at pulmonary flow rates of 350 to 400% of normal, nor the observation that pulmonary arterial pressure does not rise until pulmonary blood flow is trebled.

Early Mortality After Initial Myocardial Infarction in a Population Study (P)

Charles W. Frank, Eve Weinblatt, Sam Shapiro, and Robert V. Sager, New York, New York

This study was designed to determine the incidence and prognosis of defined clinical manifestations of coronary heart disease in an adult population of approximately 115,000. In the first 18 months of the study, 301 males and 58 females suffered an initial myocardial infarction (MI). Patients dying suddenly under circumstances meeting the definition of a new coronary event were included. The mortality rate in the four weeks following the MI was examined in relation to characteristics at the time of diagnosis. Overall mortality in this period was 32% for males and 40% for females. Prior angina, diabetes, and differences in smoking habits had no significant relation to mortality in men, but men known to be normotensive prior to the infarction had a lower mortality in the four weeks than all other men combined.

A striking positive observation was the impact of the customary pattern of physical activity upon early mortality following first myocardial infarction in men. This study had previously noted that men classified as "least active" had an excess incidence of MI. The present data indicate that among men suffering an initial MI, the "least active" experienced a mortality rate three times greater than the "most active" category. Of the 81 "least active" men, 40 were dead within four weeks (49%), in contrast with 17% of the "most active" group (15 deaths among 89 cases). This relationship of mortality rate to physical-activity class remained when age, existence of prior angina, or existence of an elevated blood pressure were controlled.

Measurement of Ventricular Volume by the Upstream-Sampling Technique in Aortic Regurgitation

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It can be shown from conventional mathematical models of indicator-dilution curves that in aortic regurgitation (AR), the slopes of upstream dilution curves recorded from the left ventricle (LV) following indicator injection into the aortic root (Ao) should equal the slopes recorded from Ao following LV injection. Thus, end-diastolic volume (EDV) can be measured, as forward stroke volume/1-slope, using Ao-to-LV rather than LV-to-Ao curves. This approach offers the advantage of simultaneity of flow and volume measurements: EDV is measured from the same dilution curve used to measure AR by the upstream-sampling technique.

Analysis of 43 cardio-green dilution curves recorded in six patients with moderate to severe AR (total flows, 5 to 20 L/min and regurgitant fractions, 0.25 to 0.64) demonstrated that volumes obtained from Ao-to-Lv curves are, indeed, comparable with those obtained from LV injections. This was true not only for slug injection into Ao with measurement of decay slope, but also for continuous infusion with measurement from the upslope of the LV curve. EDV was 141 to 266 ml from LV-to-Ao measurements, and 130 to 299 ml from Ao-to-LV. Disparities, when present, consisted of smaller ejection fractions and larger EDV from Ao-to-LV curves, suggesting that this

method of dye delivery results in enhanced LV mixing of indicator.

It is concluded that in AR, EDV can be measured not only by the classical LV-to-Ao technique, but also by Ao-to-LV dilution curves, thereby permitting simultaneous recording of the data necessary to measure end-diastolic, end-systolic, forward, and regurgitant volumes.

Effects of Smoking on Cardiac Output, Free Fatty Acids, and Catecholamines in Healthy Young Subjects During Cardiac Catheterization

William S. Frankl, Ronald H. Friedman, George T. T. Wilson, and Louis A. Soloff, Philadelphia, Pennsylvania

It has been established that smoking increases cardiac output and blood free fatty acids, and that nicotine releases catecholamines from extra-adrenal chromaffin tissues in man. An attempt was made to assay the effect of smoking in persons exposed to the stress of cardiac catheterization.

Six young, healthy subjects were studied; all were chronic smokers. Cardiac output, cardiac index, and stroke volume were determined by the dye-dilution technique. Blood free fatty acids were determined by the method of Bragdon. Blood catecholamines were determined by the trihydroxyindole fluorometric method. All these parameters were measured before smoking, during the smoking of two cigarettes in ten minutes, and after 15, 30, 60, and 90 minutes of smoking.

In five of six subjects, cardiac output was well above normal before smoking. In all six, free fatty acids were above normal before smoking. The blood catecholamines were normal for our laboratory in all six. There was no significant rise in cardiac output, stroke volume, free fatty acids, or catecholamines during and after smoking; in several instances, these parameters actually fell after smoking. Therefore, the elevations in cardiac output and free fatty acids produced by cardiac catheterization were not increased any further by smoking.

Thus, although tobacco may produce elevations in cardiac output, free fatty acids, and catecholamines in quiet, resting subjects, these studies cast some doubt on whether tobacco exerts any significant effect under nonbasal conditions.

Analysis of Serum Lipoproteins of Monkeys Fed Human Diets

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The serum of rhesus monkeys fed either a "prudent" or an "average" American diet was separated in the ultracentrifuge into three lipoprotein fractions, α-2, β, and α-1. The fractions were analyzed for total lipid, total cholesterol, ester cholesterol, and phospholipid. Extracts of these lipoprotein classes were separated on thin-layer plates, and the fatty acids of cholesterol esters, triglycerides, and phospholipids were converted to methyl esters for gas chromatography analysis. Total diet fatty acid patterns were also determined.

The lipoprotein analyses on pooled sera indicated that the cholesterol of α-1 lipoproteins from the sera of monkeys fed the "average" American diet was 64 mg%, while that from the "prudent"-fed animals was 47 mg%. Cholesterols from the β-lipoproteins were 161 and 112, and those from the α-2 lipoproteins were 9 and 2 mg%, respectively. The α-1 and β-cholesterols of the "average" American diet–fed monkeys were about 50% higher than those from the "prudent" diet–fed monkeys, while the α-2 cholesterols were 300 to 400% higher in the "average" American diet group. "Prudent" serum lipoprotein extracts had large amounts of linoleic acid, reflecting the fatty acid makeup of the diet lipid.

Effect of Hydrochlorothiazide on the Thyroid Gland and on Urinary Excretion of I^{131} in Rats

Melvin J. Fregly, Gainesville, Florida

Male rats treated with hydrochlorothiazide at dose levels of 0.3 (seven rats) and 0.6 (seven rats) g/kg of iodide-deficient diet for eight weeks had thyroid-to-body weight ratios 23% and 44%, respectively, above those of seven controls given iodide-deficient diets alone. In spite of increases in thyroid-to-body weight ratio, gross manifestations of hypothyroidism were absent, in that growth rate, resting oxygen consumption, food intake, and serum cholesterol concentration of treated rats were similar to those of controls. Urinary excretion of I^{131} was measured to determine if the increase in thyroid weight–to–body weight ratio accompanying drug administration might be associated with excessive iodide excretion. Eighteen adult male rats were used. Six were injected with 10 mg and six with 25 mg hydrochlorothiazide/kg body weight, intraperitoneally. Controls received the vehicle used to dissolve the drug. All rats received intraperitoneal injections of carrier-free NaI^{131} (7 μc) and a water load of 3% of body weight. Excretion of urine, I^{131}, sodium, chloride, and potassium was measured for five hours thereafter. Both doses of hydrochlorothiazide increased excretion of urine, I^{131} (% injected dose/5 hours), sodium, potassium, and chloride (mEq/5 hours) significantly above control levels. Treatment with hydrochlorothiazide at the dose levels used appears to induce a state of

compensated hypothyroidism which may arise initially as a result of increased urinary iodide loss.

Arrhythmias Following External Direct-Current Shock

Charles K. Friedberg, Lawrence J. Cohn, and Ephraim Donoso, New York, New York

Synchronized external d-c capacitor discharge was employed 53 times in 48 patients for the conversion of cardiac arrhythmias. Sinus rhythm was restored in 91% (48 of 53), but was maintained for at least one day in only 81% (43 of 53). The underlying cardiac disease was rheumatic in 25, arteriosclerotic in 16, and miscellaneous in 6; five patients had no apparent heart disease. Forty-five procedures were carried out while the patient was under the influence of digitalis.

There were 33 procedures in which significant new arrhythmias were seen after d-c shock, all but three involving patients on digitalis. The arrhythmias seen were (number of patients on digitalis in parentheses): ventricular fibrillation (not related to improper synchronization), 2 (2); ventricular tachycardia with ventricular bigeminy, 2 (2); nodal or idioventricular rhythm with ventricular bigeminy, 2 (2); and idioventricular rhythm, 1 (1). Ventricular premature contractions were seen 26 times. They were unifocal in 12 (10) and multifocal in 14 (13), with bigeminal rhythm in 17 (15). Nodal rhythm was seen in 6 (4), atrioventricular dissociation in 6 (6), and wandering atrial pacemaker in 5 (5).

There appeared to be a correlation of serious arrhythmias and total energy used. In only 19 of 39 procedures in which 100 joules or less were used did a serious arrhythmia develop, while this complication occurred in seven of eight procedures in which 400 joules were delivered. All serious arrhythmias subsided spontaneously or responded to therapy, including additional d-c shock. It appears that cardiac irritability is enhanced after d-c shock, and that the effects of d-c shock and digitalis on cardiac irritability are additive.

Occupational Stress, Law School Hierarchy, and Coronary Artery Disease in Cleveland Attorneys

Ernest H. Friedman and Herman K. Hellerstein, Cleveland, Ohio

The prevalence of coronary artery disease has been related to degrees of stress within an occupation. To test this hypothesis, questionnaires were mailed to 3,950 attorneys in Cleveland. There was a total return of 2,342 questionnaires (59.2%), 1,904 responses to the first mailing and 438 responses to a second mailing to nonresponders. Data processing was done on an IBM-7040 computer. Questions were similarly answered by first- and second-wave responders, suggesting that a representative sample was obtained.

Coronary prevalence was compared with stress ranks of legal specialties and the quality of the law school attended. Comparison of coronary prevalence in age-grouped (40 to 69 years), stress-ranked specialties according to Russek's criteria (general practice, $N = 679$, 7.5%; trial, $N = 84$, 4.7%; other specialties, $N = 287$, 5.2%; patent, nontrial, $N = 101$, 2.98%) demonstrated slight differences which were not significant ($P > 0.05$).

Subjects were grouped by quality of law school attended, rated independently by a law school dean. A hierarchy of four groups was established, with group I (Harvard, Yale, Columbia, Chicago, Michigan) the highest quality. Comparison of age-grouped (23 to 59 years) school groups I ($N = 307$) and III ($N = 739$) demonstrated a significant difference in coronary prevalence (I = 0.65%; III = 2.84%; $P < 0.05$). School group II ($N = 26$), mainly West Coast schools, was not used because of the small sample. School group IV ($N = 750$) coronary prevalence (2.0%), although intermediate, did not differ significantly from school groups I and III. Coronary rates among the three school groups (60 to 69 decade) were similar. Annual income, $16,000 or more, age-grouped (23 to 59 years), was as follows: I = 16.6%; III = 9.4%; IV = 5.8%; $P < 0.001$. Coronary prevalence correlated with law school quality, but not with stress-ranking of legal specialties, tending to support the social mobility concept (Hinkle).

Behavior Patterns and Serum Cholesterol in Patent Attorneys (P)

Ernest H. Friedman, Herman K. Hellerstein, Stephen E. Jones, and Gregory L. Eastwood, Cleveland, Ohio

Overt behavior patterns have been related to serum lipids and to premature development of coronary arteriosclerosis. To test this hypothesis, the authors have made a study of 107 male patent attorneys (92% of such specialists in Cleveland), consisting of a tape-recorded interview according to Rosenman's method; measurements of serum cholesterol, height, weight, and blood pressure; and a questionnaire regarding social, familial, and professional activities. The interviews were analyzed simultaneously and independently by Dr. Ray Rosenman and two of the authors (E.F. and H.K.H.).

The behavior types of the total study group were classified by Dr. Rosenman as follows: 52 subjects, type A (48.6%) and 55 type B (51.4%). One author gave the same rating in 84.1% (90/

107), and the other in 80.4% (86/107); the major discrepancy occurred in subtypes A2 or B3, who possessed significant A and B characteristics and stylistics. There was only one case with major disagreement, rated A1 by one observer and B3 by another.

For purposes of comparison with previous reports of Rosenman and Friedman, subjects between 38 and 56 years of age were studied. There were 22 subjects of type A (mean age, 45.7 years, SD 4.3); and 29 subjects of type B (mean age, 46.9 years, SD 6.01). The two groups were comparable in terms of height, weight, and pressure. The serum cholesterol of the type A group was 224.7 mg%, SD 34.0; and of the type B group it was 220.4, SD 37.9. These differences are not significant, and hence do not support the hypothesis that overt behavior patterns correlate with serum cholesterol. This study confirms the reproducibility of the technique of classifying personality according to the criteria of Rosenman and Friedman.

Vasoregulatory Asthenia: A Cause for False-Positive Exercise Electrocardiograms (P)

Gottlieb C. Friesinger, Ivan Likar, Robert O. Biern, and Robert E. Mason, Baltimore, Maryland

Fourteen patients undergoing studies for evaluation of chest pain and with clinical observations of neurocirculatory asthenia have been found to have false-positive exercise electrocardiograms. The electrocardiograms show classical "ischemic" changes, with "square-wave" S-T segment depressions of 1 mm or more during and following exercise. On clinical grounds, none of these 14 patients has coronary heart disease. Selective coronary arteriograms were performed in 11 of these patients, and the coronary arterial tree was normal in every case.

Twelve-lead electrocardiograms were recorded with the patients in the supine and standing positions and during exercise, using lightweight electrodes; responses were reproducible and similar in all cases. The response was characterized by: (1) ST-T wave shifts in leads II, III, V_4, V_5, and V_6 on standing; (2) the appearance of the "ischemic" S-T segment depression soon after the onset of exercise; (3) the absence of anginal pain in association with the ischemic S-T segment changes of exercise; (4) the return of the electrocardiogram toward normal as exercise continued; and (5) recurrence of the ischemic changes after exercise as the heart rate slows when the patient is supine. The use of elastic stockings lessened the electrocardiographic response to standing, and the performance of the Valsalva maneuver abolished the abnormalities or rendered them less prominent. A β-adrenergic blocking drug was administered to one of these patients and abolished the electrocardiographic abnormalities. A disorder of the autonomic nervous system seems to be responsible for the described changes.

Tilt Test for Investigating a Neural Component in Hypertension (P)

Edward D. Frohlich, Robert C. Tarazi, Harriet P. Dustan, and Irvine H. Page, Cleveland, Ohio

To measure autonomic nervous function in hypertension, responses to passive 60° head-up tilt, the Valsalva maneuver, and trimethaphan (0.045 mg/kg, intravenously) were studied in 22 untreated patients with various forms of hypertension. Intra-arterial pressure was recorded continuously. Cardiac output (indocyanine-green dye) was measured with the patient in the supine position, at two and five minutes' tilt, and five minutes after tilt.

On the basis of the blood pressure response to tilt, two groups were found: orthostatic hypertension (group I, 15 patients) and orthostatic hypotension (group II, 7 patients). Averages of supine mean arterial pressure, cardiac indices, and total peripheral resistances for both groups were not significantly different (127 mm Hg, 3.3 L, 0.22 P.R.U.; and 128 mm Hg, 2.8 L, 0.026 P.R.U., respectively). After five minutes' tilt, cardiac index was equally reduced (25 and 27%, respectively); however, total peripheral resistance increases were significantly different ($P < 0.05$). Group I increased peripheral resistance 56% after five-minute tilt, whereas group II increased resistance by 29%. When studied in the supine position, group I also demonstrated a significantly greater ($P < 0.05$) diastolic pressure increase during the Valsalva overshoot (43% versus 19%) and a greater ($P < 0.05$) diastolic pressure decrease following trimethaphan (16% versus 8%).

This study does not determine whether the enhanced responses of the patients with orthostatic hypertension result from increased sympathetic vasomotor outflow or from cardiovascular hyperresponsiveness to normal sympathetic outflow, but it does indicate that in some patients, neurogenic factors are important determinants of arterial pressure.

Long-Term Follow-up Study of Periarteritis Nodosa

Peter P. Frohnert and Sheldon G. Sheps, Rochester, Minnesota

During the 16 years ending December 31, 1962, 130 patients with a histological diagnosis of periarteritis nodosa were treated. The greatest incidence was in the fourth and fifth decades of

life (range, 6 to 72 years). Fever and weight loss were the most common symptoms (75% of the patients), while involvement of joints, skin, or nervous system was noted in 50 to 60%. Sixty-five patients (50%) had received ACTH or corticosteroids before admission here, and this group appeared to have a lower incidence (13 versus 24) and a less severe degree of hypertension, as well as less severe renal involvement.

During the follow-up period, 72 patients are known to have died, 33 (25% of 130) during the initial hospitalization. Of 21 patients receiving little or no treatment with corticosteroids, nine died during the first admission and four others died within the next year. Of 109 patients receiving intensive treatment, 24 died during the initial hospitalization and 12 died within the next year. The three-, five-, and ten-year survivals in the intensive treatment group were 42, 38, and 30%. The corresponding survivals among the others were 15, 6, and 0%. Treatment with steroids was continued in about half the patients surviving three and five years, and in about one-third of those surviving ten years or more. Administration of steroids greatly improves prognosis, although maintenance treatment frequently is necessary.

Congenital Abnormalities of the Aortic Valve Associated with Malformations of the Aortic Arch: An Anatomical Analysis of 112 Cases

Arthur H. L. From, Kenneth L. Jue, Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

An anatomical analysis of the aortic valve was made in 112 cases with malformations of the aortic arch including coarctation, tubular hypoplasia, or interruption. Most of the material was obtained from necropsies on infants.

Abnormalities of the aortic valve were found in 55.1% (27 of 49) of cases of coarctation, 51.9% (27 of 52) of cases of tubular hypoplasia of the arch, and 45.4% (5 of 11) of cases of interruption of the arch. The valvular malformations encountered ranged from minimal fusion at one commissure, through classical bicuspid aortic valve, to nearly complete absence of two commissures with a resultant unicuspid stenotic aortic valve. The most common abnormality found was fusion at and partial absence of one commissure with bicuspidization of the aortic valve. In many of the latter group, the malformed commissures were developed enough to result in the presence of three sinuses of Valsalva, thus making angiocardiographic diagnosis of the bicuspid valve extremely difficult.

This study demonstrates that in addition to the well-known association between aortic valvular malformations and coarctation of the aorta, there is an equally frequent association between aortic valvular malformation on one hand, and tubular hypoplasia or interruption of the aortic arch on the other. The data further suggest that the congenital bicuspid aortic valve may most commonly be a part of a complex including aortic valvular and aortic arch malformations, and that *either* component of the complex or *both* components may dominate the pathological picture.

Suppression of Ouabain-Induced Ventricular Arrhythmias by Paired Electrical Stimulation (P)

Peter L. Frommer, Brian F. Robinson, and Eugene Braunwald, Bethesda, Maryland

Pairs of electrical stimuli may be applied repeatedly to the ventricles so that the second of each pair produces a depolarization without evoking an effective contraction. Thus, two consecutive refractory periods occur with each effective contraction, permitting slowing of the heart rate and suppression of arrhythmias. The effects of paired electrical stimulation (PES) were studied in 35 anesthetized, closed-chest dogs receiving toxic doses of ouabain. In three groups of seven dogs each, ouabain was infused continuously (1 μg/kg/min) until death. The control group developed major ventricular arrhythmias at 54 ± 10 (1 SD) minutes and ventricular fibrillation (VF) at 97 ± 20 minutes. In the second group, PES was begun after the onset of arrhythmias; it suppressed the arrhythmias, produced a slower and regular effective heart rate which was maintained until VF occurred at 90 ± 10 minutes. In the third group, PES begun before the ouabain infusion prevented all arrhythmias until VF occurred at 73 ± 12 minutes. To simulate clinical circumstances, a single toxic dose of ouabain (70 μg/kg) was given to 14 dogs; ten were treated with PES and four were controls. Survival in these groups was comparable (eight of ten, three of four), but PES effectively suppressed arrhythmias and slowed the heart rate from an average of 226 to 137/minute. When PES was discontinued after two to six hours, the toxic effects of the glycoside had disappeared or waned. Although it is not without hazard, PES effectively suppresses digitalis-induced arrhythmias and may prove useful in selected clinical instances of digitalis intoxication.

Myxedema: A Cause of Reversible Hypertension (P)

Henry Fuller, Jr., John A. Spittell, Jr., William M. McConahey, and Alexander Schirger, Rochester, Minnesota

Although the association of myxedema and hypertension has been reported, myxedema is not

usually considered to be a cause of reversible hypertension. This study was undertaken to determine: (1) whether hypertension associated with myxedema resolved during thyroid replacement therapy; and (2) what characteristics, if any, would enable us to predict whether the hypertension would resolve during therapy of the myxedema only.

Of 101 patients with hypertension and myxedema seen between 1959 and 1963, 92 were available for follow-up. There were 77 patients with diastolic hypertension (16 men and 61 women); of these, 22 became normotensive with only restoration of euthyroidism and without antihypertensive therapy; 11 patients required only a thiazide diuretic to control the hypertension. Among 15 patients with systolic hypertension, six became normotensive following treatment of myxedema alone; the blood pressure of an additional patient was well controlled with a thiazide diuretic alone after the myxedema had been corrected.

Although our study showed no absolute means of prediction, in general the younger the patient the shorter was the duration of hypertension; and the higher the concentration of blood cholesterol the more likely it is that the patient may become normotensive with treatment of myxedema alone. The basal metabolic rate, protein-bound iodine value, type of hypertension, and duration of myxedema seemed to have no predictive value regarding the outcome.

Respiratory-Gas Delivery System for Hyperbaric and Ward Use

Robert L. Fuson, Wirt W. Smith, and Herbert A. Saltzman, Durham, North Carolina

The effectiveness of medical gas therapy in dyspneic cardiac patients is often hampered or nullified completely by delivery-system discomfort or inefficiency. Therefore, an efficient respiratory-gas delivery system has been developed which is easily tolerated by dyspneic, tachypneic patients. Thirty-six L/min of gas circulate through a clear, plastic head tent, carbon dioxide absorber, and heat exchanger. The head-tent seal adheres to the upper thorax, allowing unimpeded vision and vocal communication with the patient. In use, this system has an internal carbon dioxide concentration of less than 0.06%, and a mean oxygen concentration of 97% during single gas administration. Concomitant mean arterial blood gas values with 100% oxygen administration are: 610 and 34 mm Hg, respectively, for pO_2 and pCO_2 at 1 atmosphere absolute (atm abs), and 2,150 and 35 mm Hg, respectively, at 3.04 atm abs. Only 1.6 L/min of oxygen are required to replenish the internal volume of the delivery apparatus. These observations confirm the efficiency and acceptability of this system for medical gas therapy of dyspneic cardiac patients at normal and increased atmospheric pressures.

Experimental Large-Volume Hemodilution with Plasma (P)

Howard L. Gadboys, Robert S. Litwak, Melvin Kahn, Shaul Kochwa, and Wiltrud E. Buerger, New York, New York

Hemodilution with crystalloidal solutions has ameliorated many sequelae of the homologous blood syndrome. However, previous experimental studies have shown that constant-volume dilutional exchange (100 ml/kg) leads to severe hypotension and acidosis. Thirty-six normothermic constant-volume exchanges were carried out in dogs. Control studies with small volumes of diluent (10 to 20 ml/kg) in 15 dogs revealed hemodynamic and biochemical stability of the experimental model.

Exchange of 2.5% albumin in Ringer's solution (100 ml/kg) caused severe, persistent hypotension (mean fall, 61% of control) and acidosis in each of five animals. Autologous plasma (mean albumin concentration, 2.0 g%) was dialyzed against Ringer's solution and exchanged under identical circumstances (100 ml/kg), and no hypotension (mean blood pressure remaining within 20% of control) or acidosis (mean base excess, +1.0 mEq/L) was observed. *Fresh homologous plasma* (100 ml/kg) produced no hypotension (mean blood pressure remaining within 10% of control) or acidosis. Dialyzed homologous plasma caused transient hypotension (mean fall, 39% of control) and 3.9 mEq/L base deficit.

The observed hypotension, either persistent (Ringer's-albumin) or transient (dialyzed homologous plasma) could not be explained by the insignificant changes of cardiac output ($\Delta \pm 0.2$ L/min). Attempts are being made to isolate and characterize the dialyzable substance, the removal of which causes hypotension during exchange with dialyzed homologous, but not autologous, plasma. The data suggest that plasma as a perfusate is superior to crystalloidal diluents of equivalent ionic, oncotic, and viscosity properties, because of observed better hemodynamic and biochemical stability.

Long-Term Results with an Implanted Pacemaker (P)

Andrew A. Gage, Anthony J. Federico, George Schimert, Buffalo, New York, Wilson Greatbatch, Clarence, New York, and William M. Chardack, Buffalo, New York

Treatment of complete heart block with an implanted pacemaker has now been used by us in

100 patients. Seventy-five were between the ages of 60 and 89 years. Nine postoperative deaths and 18 late deaths have occurred from myocardial infarction (four), congestive failure (five), unrelated causes (four), unknown causes (three), and pacemaker failure (two). Late deaths occurred 1 to 44 months postoperatively (mean, 16 months). Seventy-three patients are alive and pacemade from 1 to 60 months postoperatively (mean, 25 months). Rehabilitation was gratifying, and our data now show definite prolongation of survival of pacemade patients. Of 16 patients created four or more years ago, eight are alive, and the seven late deaths in this group occurred between 5 and 44 months postoperatively (mean survival, 25 months), in contrast with a 50% first-year mortality rate reported for comparable but not pacemade patients.

Electrode failure (steel wire) required 13 repeat thoracotomies in the first 16 patients, but only two have been performed since introduction (1961) of electrodes with a coil structure.

Analysis of pulse-generator performance in this series and in 8,000 units of the same design used by others has revealed that component failure has been higher than expected. However, data on instrumentation manufactured since January, 1964, indicate significant and continuing improvement in performance.

Long-term correction of complete heart block can be achieved by fixed-rate, asynchronous ventricular pacemaking with an implanted device. Rehabilitation and prolongation of survival are impressive.

Clinical Assessment of Aortic Regurgitation: A Comparison of Two New Methods—Fiberoptic Indicator Dilution and Vectorcardiographic—with Conventional Criteria

Walter J. Gamble, Charles G. LaFarge, Paul G. Hugenholtz, Henry R. Wagner, and Alexander S. Nadas, Boston, Massachusetts

Following injection of indocyanine-green into the pulmonary artery, stepwise increases and decreases of dye concentration are found in the ascending aorta with a rapidly responding fiberoptic hemoreflection system (response time, 0.1 second). During the downslope of the dye-dilution curve, diastolic increases in dye concentration were found only if the aortic valve was incompetent.

A relationship was found between the ratio total stroke volume (TSV): forward stroke volume (FSV) and the changes of indicator concentration.

$$\frac{TSV}{FSV} = \frac{\sum_1^n (leDC) - \sum_1^n (leSC)}{(leDC)_n - (leDC)_{n+1}}$$

where leDC = log end-diastolic concentration
leSC = log end-systolic concentration.

The degree of aortic regurgitation was calculated by this method (R-ID) in ten patients and the results were compared with the ratio (R) of TSV determined by biplane angiography to FSV calculated by standard output determination methods (R-A, CO). Eight of the ten results fell across the line of identity. When the average of the indicator-dilution results (R-ID) was compared with the average of the R-A, CO, the correlation coefficient was 0.82. This is contrasted by correlation coefficients of $r = 0.07$ for the comparison of R-A, CO with central aortic pulse pressure, of $r = 0.45$ with end-diastolic volume/m^2, $r = 0.46$ for aortic diastolic pressure, and $r = 0.76$ for left ventricular end-diastolic pressure. A satisfactory correlation ($r = 0.92$) was also found when the ratio of the magnitude of the QRS spatial vector (Frank lead system) at 0.02 second, divided by the sum of the maximum spatial vector plus the spatial vectors occurring 0.01 second before and after the maximum vector was compared with R-A, CO. These techniques afford a new approach to the vexing problem of the assessment of the severity of aortic regurgitation.

Chronic Complete Heart Block Following Replacement of the Aortic Valve: Experiences and Anatomical Basis (P)

Paul G. Gannon, Robert D. Sellers, Minneapolis, Minnesota, Vladimir I. Kanjuh, Jesse E. Edwards, St. Paul, Minnesota, and C. Walton Lillehei, Minneapolis, Minnesota

In our initial experience with the first 16 cases of aortic valve replacement with the ball-valve prosthesis, chronic postoperative complete heart block resulted in four instances. This led to these studies on the anatomical relationship between the aortic valve and the major trunks of the conduction tissue. The anatomical studies show a particularly close relationship between the adjacent portions of the right and posterior (noncoronary) segments of the aortic valve on the one hand, and the bundle of His on the other.

Bearing these relationships in mind during operation, we achieved a significant reduction in the incidence of chronic complete heart block following replacement of the aortic valve. In the 182 cases of replacement by the Starr-Edwards valve following the initial experience, the incidence of chronic complete heart block has been about one out of every ten cases.

In an additional 52 cases, each operated on since the initial experience, the Magovern (sutureless) prosthesis was used to replace the aortic

valve. In this group, complete heart block occurred in five cases, but it proved to be permanent in only one (2%).

Microchemical Measurement of Tissue Enzymes in Early Rat Hypertension (P)

Dugald L. Gardner, Edinburgh, Scotland, and Christine P. Laing, Vancouver, British Columbia, Canada

This paper reports chemical measurements and histochemical assessments of enzyme activity in microsamples of heart and mesenteric arteries from rats with very early steroid hypertension when blood pressure was rising quickly, but when arterioles appeared normal microscopically. Forty-eight 200-g male rats were divided into hypertensive, normal, uninephrectomized, and salt-loaded groups. Four-mm cubes of heart muscle were quenched at −65 C. Cryostat sections were cut and freeze-dried, giving five 30-μg samples for chemical measurements; 8-μ sections were prepared for histochemistry. Alkaline phosphatase (APase) was measured colorimetrically and demonstrated microscopically by coupling–azo dye technique. Oxidative enzymes were measured fluorimetrically and demonstrated microscopically by using tetrazolium salts. In an identical additional experiment, 200-μ diameter mesenteric arteries were studied.

Histochemical results showed APase activity in coronary and mesenteric artery adventitia, in cardiac capillaries, and in intercalated discs. Lactate dehydrogenase activity appeared high in heart muscle, in arterial muscle, and in endothelium; malate dehydrogenase was moderately active in cardiac and arterial muscle and in endothelial cells; glucose-6-phosphate dehydrogenase (G-6-PDH) activity was slight in heart muscle and minimal in arteries. Microscopic comparison between hypertensive and control animals revealed no visible differences in the activity of the four enzymes studied. Microchemical analyses, however, showed decreased APase and increased G-6-PDH activity in hypertensive hearts, increased APase and increased G-6-PDH activity in hypertensive arterioles.

The results suggest that subtle changes in cardiovascular metabolism, not detected by conventional microscopy, occur in the earliest stages of rat hypertension, at a time when arterioles appear intact structurally.

Work of Breathing Following Open-Heart Surgery for Acquired Valvular Disease (P)

Antonio A. Garzon, Bernard Selzer, and Karl E. Karlson, Brooklyn, New York

Respiratory work, pulmonary compliance, and airway resistance were measured in 20 patients before and after open-heart surgery for acquired valvular disease. Many of them required controlled mechanical respiration for several days in the postoperative period. Intrathoracic pressure was determined with an esophageal balloon; respiratory flow was monitored with a pneumotachograph and integrated into volumes by a Sanborn Respiratory Preamplifier. Work of breathing and compliance were obtained from pressure-volume loops, either by planimetry or by a modification of the Otis formula. Resistance was subtracted electronically from the compliance by the respiratory preamplifier.

The mean preoperative values for compliance, resistance, and work were abnormal, but there was no significant difference between surviving (13 cases) and nonsurviving patients. However, on the first or second postoperative day, the fatal cases had a drop in compliance from 0.106 L/cm H_2O to 0.056 L/cm H_2O, a rise of resistance from 3.43 cm H_2O/L/sec to 4.82 cm H_2O/L/sec, and an increase of work from 1.015 kg-m/min to 5.515 kg-m/min. Surviving patients had a smaller drop in compliance (from 0.113 L/cm H_2O to 0.076 L/cm H_2O), a similar resistance (from 2.68 cm H_2O/L/sec to 2.64 cm H_2O/L/sec), and a slight increase of respiratory work (from 1.182 kg-m/min to 1.604 kg-m/min). This trend was maintained for seven or eight days, then began to return to preoperative values.

Measurement of Blood Flow in the Brachial Artery in Conscious Subjects by an Electromagnetic Flowmeter (P)

James H. Gault, John Ross, Jr., and Dean T. Mason, Bethesda, Maryland

Although plethysmography permits intermittent measurement of mean blood flow in the extremities, little is known about phasic arterial flow patterns, or about instantaneous flow changes in conscious human subjects. An electromagnetic flowmeter probe was placed about the exposed brachial artery in 39 patients undergoing retrograde arterial catheterization. In subjects without left ventricular dysfunction, the flow contour during systole closely resembled that of the arterial pressure pulse, while a significant, stable level of flow occurred during diastole. In four patients with hypertrophic subaortic stenosis, and in three with severe mitral regurgitation, a striking, abnormal decline in flow occurred during mid and late ejection. In eight patients with aortic regurgitation, flow fell continuously during diastole, but retrograde flow occurred in only three patients with marked regurgitation. During single voluntary hand contractions in eight patients, flow fell markedly and often ceased completely; with rhythmic contractions, flow initially declined, then increased above control levels as exercise

was continued. Stimulation of low-pressure baroreceptors by passive leg elevation (ten patients) or by electrical stimulation of the right atrium (three patients) resulted in rapid decreases in forearm vascular resistance (−20% and −43% of control, respectively), while brief, transient increases (+133%) occurred during the Valsalva maneuver (four patients). The technique described allows definition of normal and abnormal phasic flow patterns in the brachial artery and permits elucidation of the influences which cause instantaneous alterations of blood flow and vascular resistance in conscious subjects.

Carbohydrate Metabolism in Acute Myocardial Infarction

Maxwell L. Gelfand and Maximilian Fabrykant, New York, New York

Ischemic heart disease has been shown, in both clinical and necropsy studies, to be more common in diabetic than in nondiabetic persons. However, the significance of the relationship between latent or preclinical diabetes and coronary arterial disease has not received adequate attention.

In 1964, we studied a group of 42 patients, aged 42 to 66 years, who had well-documented angina with no clinical symptoms of diabetes, no fasting hyperglycemia or glycosuria, who demonstrated abnormal oral glucose tolerance tests, indicating the existence of latent diabetes. Herman and Gorlin, using intravenous glucose tolerance tests in young premature coronary patients, have corroborated our observations. Cohen and Shafrir found an impaired glucose tolerance test in the majority of 43 patients below the age of 50 with acute myocardial infarction who had no history of diabetes or fasting hyperglycemia.

We have studied the carbohydrate metabolism of 33 patients of all ages with acute myocardial infarction who had no history of diabetes, normal fasting blood sugar, and no glycosuria. They were studied three to five weeks after the onset of the infarction, using the standard oral glucose loading test. Twenty-seven of the 33 patients demonstrated a rise of the blood sugar after two hours to over 130 mg%, indicating the existence of latent diabetes. Both the younger and the older members of our group showed high glucose tolerance curves. The significance of this observation and the possible relation of latent or preclinical diabetes to coronary arterial disease was also studied.

Methicillin and Other Semisynthetic Penicillins in the Management of Staphylococcal Endocarditis

Joseph E. Geraci, Robert L. Frye, and Jack L. Titus, Rochester, Minnesota

Twenty-five patients aged 4 to 72 years (16 males, 8 females) were given methicillin to test its efficacy in staphylococcal endocarditis. Twenty had *Staphylococcus aureus* and five had coagulase-negative staphylococcal infections. Twelve infections were "medical" (did not follow cardiac operations); 13 were "surgical" (followed cardiac operations: prosthetic valve replacement, 7; valvular commissurotomy, 2; atrial and ventricular septal repair, 1 each; and superior vena caval and aortic Teflon-graft replacement, 1 each). Five of 25 patients received methicillin for one to five days until studies indicated a *Staphylococcus* sensitive to penicillin G; therapy was then changed to penicillin G. All 12 "medical" patients were cured (100%—nine with methicillin therapy and three with penicillin G alone). Of 13 "surgical" infections, seven were not cured (54%) and six were (46%). Five failures represented prosthetic valve replacements. Cure followed reoperation in one patient on removal of a small vegetation from a pericardial-patch repair of a ventricular septal defect after unsuccessful, lengthy (1+ years) therapy with methicillin and oxacillin, and followed methicillin therapy in five (two with aortic valve prostheses, two with aortic and superior vena caval Teflon replacements, and one with atrial septal defect repair). Eighteen of 25 infections were cured (72%). Results of serum assays and serum bactericidal tests indicate that 1 g of methicillin, given parenterally every three hours for 30 days, usually constitutes a minimal bactericidal program for penicillin G–resistant staphylococcal endocarditis.

Does Hypertension Truly Increase the Risk Rate of Ischemic Heart Disease? (P)

Menard M. Gertler and Harvey H. Whiter, New York, New York

There is no doubt that the risk rate of ischemic heart disease rises with increasing levels of serum cholesterol. However, there is thought by several investigators that hypertension not only increases the risk rate to ischemic heart disease, but certainly greatly enhances the risk rate to ischemic heart disease in the presence of an increased level of serum cholesterol. This presentation, based on 490 meticulously studied normal executives, does not confirm the suggestions made in the literature. This study evaluated the risk rates of the 490 men at levels of blood pressure below the mean, one standard deviation above the mean, and two standard deviations above the mean with and without the concomitant influence of serum cholesterol levels below the mean, one standard deviation above the mean, and two standard deviations above the mean. When the data are critically analyzed and the influence of each variable is considered by itself, it is evident that the risk rate to ischemic heart disease is absolutely

not influenced by the presence of hypertension. The evidence shows a risk rate of 100 for hypertension alone at all levels, while the risk rate rises from 10 to 600 as serum cholesterol levels rise from below the mean values to above the mean plus two standard deviations. When cholesterol and blood pressure are analyzed critically at varying levels and combinations, the resultant analyses are not statistically significant.

Incorporation of Exogenous Phosphate (P^{32}) into Serum Phospholipids and Cholesterol into Serum, Liver, and Aorta Lipids of Rhesus Monkeys

Godfrey S. Getz, Randolph H. Hughes, Laurence E. Frazier, and Robert W. Wissler, Chicago, Illinois

Six rhesus monkeys, fed for two years on either an average American (Av) or a prudent (Pru) diet, were injected intravenously with radioactive inorganic phosphate (0.67 mc) 48 hours before death. They also received 7.3 μc cholesterol-C^{14} orally at daily intervals for two days before death. Blood samples were taken 24 hours after isotope administration and at autopsy. The specific activity of the serum phospholipids (Pl) was similar in all animals, but since the Av animals had 1.5 to 2.5 times more Pl than the Pru animals, the percentage of administered phosphate incorporated into Pl was twice as great in Av as in Pru animals. This suggests that the higher Pl in Av animals was maintained by a higher rate of synthesis. Lipoprotein fractions prepared from serum pooled from two animals in each group revealed that the phospholipids of the high-density lipoproteins (HDL) had slightly higher specific activity than those of the low-density lipoproteins (LDL). This is probably due to the presence of relatively more sphingomyelin, which is synthesized slowly, in LDL. Composition of the phospholipids of serum, lipoprotein fractions, liver, and aorta were studied.

The percentage of administered cholesterol recovered in the serum cholesterol was variable, but tended to be slightly lower in the Pru animals, possibly because of the smaller dilution by the lower amount of dietary cholesterol in the prudent diet. The specific activities of serum free and ester cholesterol were identical, as were the activities of the cholesterol of HDL and LDL. However, the specific activity of the serum cholesterol was one to five times higher in the Pru than in the Av animals. The rate of cholesterol uptake by the aorta of each monkey was also studied.

Simultaneous Red Cell and Plasma Protein Indicator-Dilution Curves During Human Heart-Lung Bypass (P)

Stanley Giannelli, Jr., Stephen M. Ayres, and William I. Wolff, New York, New York

Indicator-dilution curves have been obtained in six patients during heart-lung bypass. Injection was made into the arterial line and sampling was from the venous return line. Instantaneous determinations of vascular volume were obtained from the product of flow rate and mean arrival time of the indicator; the latter was determined from a semilogarithmic plot of indicator concentration against time. Correction was made for the included volume of tubing. Simultaneous injection of Cr^{51}–red cells and Fe^{59}–plasma proteins was made, and the different volumes of the peripheral circulation which are reached by circulating red cells and by plasma were measured. Under conditions of normothermia, flow rate of 2.2 L/min/m^2, arterial pCO_2 of 24 to 29 mm Hg, and venous pressure of 10 mm Hg, the red cell distribution volume was 19 to 24 ml/kg. In each subject, there was an additional 5 to 20% of vascular volume that was perfused by plasma but not by red cells. This additional plasma-space measurement represents confirmation of the lower value for total-body than for large-vessel hematocrit in the peripheral circulation.

Prevalence of Congestive Heart Failure in Two Rural Communities

Thomas C. Gibson, Burlington, Vermont, Kerr L. White, Baltimore, Maryland, and Lawrence Klainer, Washington, District of Columbia

The purpose of this study was to document the prevalence of congestive heart failure as seen by the physician in the community. Two predominantly rural counties were selected, and all physicians who were likely to give medical care to the 36,578 white residents of these counties were asked to fill in a standard questionnaire on all patients with heart disease seen during a six-month period. The questionnaire was designed to obtain information concerning etiology, signs and symptoms, therapy, and the presence or absence of congestive heart failure.

It was found that the six-month period prevalence rates for congestive heart failure were, respectively, 8.8 and 10.2 per 1,000 of the white population of Montgomery County, North Carolina, and Caledonia County, Vermont. Age-specific rates demonstrated the remarkable increase in congestive heart failure with increase in age. Six-month period incidence rates for congestive heart failure occurring in patients aged 45 years and over were 1.9 per 1,000 of the white population

in Montgomery County and 2.5 in Caledonia County. The distribution of disease categories for patients with congestive heart failure was similar for both counties. Atherosclerotic heart disease and hypertensive heart disease, either separately or combined, accounted for 88% (311 of 352) of the diagnoses.

Congestive heart failure is, and will remain, a considerable chronic disease problem, especially among older people. Extrapolation of data from this study indicated that by 1970 there will be some 1,700,000 persons aged 45 years and over who are, or have been, in congestive heart failure.

Nephrectomy for Hypertension: Results in Forty-five Patients with Unilateral Renal Atrophy (P)

Ray W. Gifford, Jr., Lawrence J. McCormack, Cleveland, Ohio, and Eugene F. Poutasse, Norfolk, Virginia

Since 1955, 45 patients with renal atrophy (< 100-g kidney) have been followed for at least six months (average, 42 months) since nephrectomy for hypertension. Excellent results (blood pressure < 150/100 mm Hg without treatment) were obtained in 17 patients (38%); good results (diastolic blood pressure < 100 mm Hg with residual systolic hypertension without treatment) in 9 patients (20%); fair results (diastolic blood pressure reduced at least 20 mm Hg, but not below 100 mm Hg without treatment) in 15 patients (33%); and no relief of hypertension in 4 patients (9%). Of 26 patients with excellent or good results (group A), pyelonephritis was demonstrated in eight kidneys; of 19 with fair or poor results (group B), pyelonephritis was demonstrated in six kidneys. Ischemic atrophy from renal arterial disease (demonstrated by angiography) was present in 14 patients in group A and in 13 in group B. Four atrophic kidneys in group A appeared normal histologically (hypoplastic kidneys?). Five of six patients whose atrophic kidneys showed no intrarenal vascular disease were normotensive postoperatively. Atrophic kidneys did not visualize on intravenous pyelograms in 6 of 26 patients in group A and in 8 of 19 in group B. The best prognostic indexes were age of patient and duration of hypertension. In group A, 24 patients were younger than 50 years and/or had hypertension for less than two years, while this was true for only 9 of 19 in group B. Of 16 patients younger than 50 years, with hypertension for less than two years, 13 were normotensive postnephrectomy. Of 12 patients 50 years of age or older, with hypertension for two years or longer, none was normotensive postnephrectomy.

Oxygen Transfer During Early Exercise

Robert Gilbert, J. Howland Auchincloss, Jr., and Gerhard Baule, Syracuse, New York

The time course of the rise of oxygen transfer at the start of exercise is considered a reflection of the response of the cardiac output, but the shape of the curve has not been investigated systematically. Nine normal subjects were studied during treadmill exercise with a respiratory circuit designed for breath-to-breath measurement of oxygen transfer at the alveolar-capillary membrane (TD). The rise of TD at the start of exercise is a two-phase curve; there is a rapid initial rise, a slower secondary rise, and, in six subjects, a notch between the two phases. Repetition of the test up to 12 times with curve averaging excluded technical artifacts in the production of the notch. The steady state occurred within two minutes.

A mathematical model demonstrated that the rise of TD at the start of exercise is determined primarily by the relationship between the rise of total-body oxygen consumption and the rise of cardiac output. When cardiac output rose faster than oxygen consumption, curves of TD were similar to the experimental curves, including the notch between the two phases. In seven normal subjects, during treadmill exercise, cardiac output measured by the indicator-dilution technique reached a steady state within two minutes in four, three minutes in two, and four minutes in one. The results suggest that body oxygen consumption may rise more slowly than cardiac output at the start of exercise and may take more than one minute to reach a steady state during even mild exercise.

Use of Propranolol in Cardiac Arrhythmias

William M. Ginn, Jr., George V. Irons, Jr., and Edward S. Orgain, Durham, North Carolina

Propranolol is an adrenergic β-receptor blocking drug possessing 10 to 20 times the β-receptor blocking action of its predecessor, pronethalol. Propranolol was administered intravenously to 34 patients to evaluate its effect on the following arrhythmias: (1) sinus tachycardia (ten); (2) atrial fibrillation (four); (3) atrial flutter (four); (4) frequent ventricular ectopic contractions not related to digitalis (four); (5) paroxysmal atrial tachycardia unrelated to digitalis (two); and (6) arrhythmias resulting from digitalis intoxication—paroxysmal atrial tachycardia with block (five) and multiple ventricular ectopic contractions (five).

Propranolol was administered intravenously in doses ranging from 2 mg to 10 mg during continuous electrocardiographic monitoring. After

intravenous propranolol, nine of ten patients presenting sinus tachycardia slowed within ten minutes to less than 100 beats per minute. All seven patients exhibiting paroxysmal atrial tachycardia, secondary to digitalis intoxication in five, reverted to normal sinus rhythm. No change was noted in the atrial rate of four patients exhibiting atrial flutter. In two instances of atrial flutter and two instances of atrial fibrillation presenting ventricular rates greater than 100 beats per minute, there was definite slowing of the ventricular rate. In each of five patients exhibiting frequent ventricular ectopic contractions related to digitalis, the ectopic contractions were abolished; but in four additional patients, ventricular ectopic contractions unrelated to digitalis were unaffected by the drug.

Propranolol provides effective slowing of sinus tachycardia, rapid conversion of paroxysmal atrial tachycardia—with or without intoxication—to normal rhythm, and suppression of ventricular ectopic contractions caused by digitalis.

Brain Scans of Cerebral Infarcts (P)

Joseph L. Glasgow, Robert D. Currier, Jack K. Goodrich, and Forrest T. Tutor, Jackson, Mississippi

The results of over 140 scans of the cranial vault in patients with a final clinical diagnosis of cerebral infarct, including four probable hemorrhagic infarcts, with Hg^{203}- or Hg^{197}-chlormerodrin are presented. All patients admitted to the hospital with a clinical diagnosis of stroke since April of 1964 were scanned and are included; all scans of infarcts at the Medical Center since 1962 are also reviewed. Nearly half of the scans were positive. It was found that three major factors influence radioactive-Hg uptake in patients with infarcts: time, size, and location. About one-third were positive if done in the first two weeks, 80% (20 of 25) were positive in the third week, followed by a sharp decrease to one-third positive in the fifth week, with a further decrease until, six months after the ictus, no uptake was found. Clinically, small infarcts did not show up well, if at all. Infarcts in the distribution of the anterior cerebral, posterior cerebral, and basilar vertebral systems were more difficult to visualize. Patients with a negative scan at the three-week interval recovered well from the stroke. Position and size of the infarct correlated well with the clinical examination. Infarcts, compared with brain tumors, were usually easily differentiated by: (1) degree of uptake relative to size of the abnormal area; (2) indistinct border of the lesion in cerebral infarcts; and (3) configuration and position of the abnormal area. However, an occasional infarct scan gave the appearance of tumor, and infarcts were sometimes suggestive of subdural hematomas.

Influence of Diastolic Augmentation on Myocardial Revascularization Following Acute Coronary Occlusion

David Goldfarb, Gottlieb C. Friesinger, and Walter F. Ballinger, II, Baltimore, Maryland

The influence of diastolic augmentation upon myocardial revascularization following acute coronary occlusion and massive myocardial infarction has been studied in 12 dogs. Selective coronary cineangiograms were performed before and at intervals following ligation and division of the anterior descending coronary artery near its origin. Survivors were sacrificed at ten weeks. No treatment was instituted in a control group of seven animals. Diastolic augmentation was applied for two hours after ligation in the remaining five dogs. All hearts were examined for histological changes.

Three of the control dogs died of ventricular fibrillation following occlusion. In three others, the entire area below the point of ligation demonstrated massive myocardial infarction. Inadvertently, in the remaining dog, the artery was ligated only beyond the terminal bifurcation; reconstitution of this distal artery occurred. One of the treated animals died of ventricular fibrillation following coronary occlusion. Partial or complete revascularization and viability of the myocardium deprived of its natural blood supply was demonstrated histologically in the remaining four. Coronary cineangiography in one dog four hours after augmentation and in another ten weeks later revealed retrograde flow through the coronary artery distal to the occlusion. In this ten-week survivor, before sacrifice, myocardial oxygen tensions proximal and distal to the occlusion were identical.

These early results suggest that diastolic augmentation might serve to influence myocardial revascularization and viability following acute coronary arterial occlusion.

Rapidity of In Vivo Renal K^{42} Exchange (P)

Arthur G. Goldman, A. Aaron Yalow, Morris Wolfman, and Harold Garelick, New York, New York

Burg and Orloff reported that the exchange of K^{42} with the "large" K compartment of separated renal tubular cells has a half-time of seven minutes, compared with 27 to 30 minutes for tissue slices. To investigate whether in vivo exchange was even more rapid, K^{42} was injected into the right renal artery of anesthetized dogs undergoing

osmotic diuresis, and the specific activity of right ureteral urine was assayed at frequent intervals for 15 minutes. Urinary specific activity peaked at 60 to 80 seconds; the semilogarithmic plot curved for approximately five minutes and was essentially linear thereafter. From λ', the slope of the linearly descending portion corrected for a small amount of re-entering arterial plasma radioactivity, the effective renal plasma flow (C_{PAH}), and arterial plasma potassium concentration $[K^{39}]_{ap}$, the exchanged pool of renal K (K_{ex}) was calculated:

$$K_{ex} = [K^{39}]_{ap}\ C_{PAH}/\lambda'.$$

This was compared with the total right kidney K^{39} content ($K^{39}{}_{obs}$), and expressed as per cent renal K exchanged: $[K_{ex}/K^{39}{}_{obs}]$. In seven studies in five dogs, λ' averaged 0.20 ± 0.06 (SD)/min. K_{ex} approached 100% of renal K (average, $K_{ex}/K^{39}{}_{obs} = 92.7 \pm 5.3\%$). Although the linear portion of the urinary specific activity curve, which determined K_{ex}, began at five minutes, the slowest capillary and tubular transits were represented. Hence, intrarenal K^{42} exchange must have occurred considerably earlier, possibly within the time of a single passage through a nutrient capillary bed. In addition to geometrical advantages over in vitro systems, K^{42} exchange in vivo may be enhanced by the metabolically stimulating effect on proximal tubules of active reabsorption of filtered sodium.

Cineradiographic Observations on the Pattern of Pulsatile Blood Flow in the Pulmonary Circulation of the Dog (P)

Harold S. Goldman, Eugene Morkin, and Alfred P. Fishman, New York, New York

Radiographic approaches to the study of the pulmonary circulation have been concerned chiefly with the anatomy of the arteries and veins or with distortions of the anatomy by abnormal stimuli. In this investigation, cineradiography has been used to study pulsatile blood flow in the pulmonary circulation. Twenty narcotized, lightly anesthetized, spontaneously breathing dogs were studied cineradiographically in the supine position. Seventy-five per cent diatrizoate sodium was injected through catheters positioned fluoroscopically into the pulmonary artery, pulmonary arterial "wedge" position, pulmonary venous "wedge," and pulmonary vein; injections were also made into one pulmonary artery distal to an occluding balloon. A radiopaque marker activated by the R wave of the electrocardiogram was used to indicate the phase of the cardiac cycle.

It was observed that: (1) flow is pulsatile in all visualized arteries and veins; (2) the arterial vessels expand during each systole, while the larger veins remain nearly constant in diameter; (3) the principal forward surge of contrast material in the veins occurs during the phase of reduced ventricular ejection and follows that in the arteries by about 0.09 second; (4) there is atriovenous "reflux" during atrial systole; and (5) injections of contrast material distal to an occluding balloon in one pulmonary artery showed slow runoff, with no pulsatility except that due to atriovenous reflux. These results indicate that the flow pulse generated by the right heart is primarily responsible for the flow pattern observed throughout the pulmonary circulation, there being no major effect of the left heart on the forward surge in venous flow. In addition, no evidence was found for the existence of sphincter-like action at the venoatrial junction.

Role of Myocardial Norepinephrine Stores in the Contractile Response of the Hyperthyroid Heart

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Published reports on in vitro studies indicate a decreased myocardial contractility in hyperthyroid animals. The observation of increased norepinephrine (NE) stores in hyperthyroid guinea pig myocardium raises the question of the role of these stores in the contractile response. Comparison of left ventricular end-diastolic pressure (LVEP) and peak systolic pressure (PSP) during graded aortic obstruction served as a measure of the myocardial contractile response in the normal and hyperthyroid guinea pigs studied. To compare "pressure-function" curves so obtained, the PSP at an LVEP of 15 mm Hg was selected as an index of response (P_{15} index).

Hyperthyroid left ventricles had a P_{15} index of 183 ± 4 mm Hg, compared with the normal control value of 138 ± 5 mm Hg ($P < 0.001$). The resting maximum rate of rise of left ventricular pressure (dP/dt) for the hyperthyroid ventricles was 2,700 mm Hg/sec, and that of normal controls, 1,000 mm Hg/sec ($P < 0.001$). Reserpine pretreatment of hyperthyroid guinea pigs produced a significant fall in contractility as measured by the P_{15} index and dP/dt, but both parameters were still significantly higher than the normal controls ($P < 0.001$), despite an almost complete absence of NE stores in the reserpinized hearts. Hyperthyroid hearts also showed both an increase in resting rate and an increase in chamber weight above normals.

The observations are consistent with the view that, although NE stores in the myocardium play a role in the increased contractility observed in hyperthyroid hearts, other factors, including heart

rate and hypertrophy, may contribute to this increase.

Renal Function in High-Flow Hemodilution Perfusion

Berney Goodman, Robert S. Litwak, Howard L. Gadboys, Helene Brooks, and Melvin Kahn, New York, New York

Increased urinary flow observed during and after open-heart surgery since the introduction of hemodilution perfusion has been interpreted as indicating improved kidney function. To evaluate this suggestion, 45 patients undergoing high-flow, whole-body hemodilution perfusion were studied. Half the priming perfusate was acid-citrate-dextrose (ACD) blood. In 32 cases, the remaining 50% was dextrose/Ringer's/albumin/THAM [tris (hydroxymethyl) aminomethane] solution (B-DRAT); in 13 cases, plasma/THAM (B-PT). THAM in the B-DRAT group was double that in the B-PT group. Perfusion time approximated two hours in both groups.

In the B-DRAT cases, despite a high perfusate concentration of sodium and chloride, plasma levels of these electrolytes dropped to below control values during early perfusion, suggesting a dilutional increase in extracellular volume which appeared to be related to the marked hypertonicity of the perfusate (456 mOsm/kg). Subsequently, plasma electrolytes were stable except for a variable postoperative hypochloremia attributable to the obligatory excretion of chloride with cationic THAM. These alterations were not observed in the B-PT cases, since the perfusate was less hypertonic (310 mOsm/kg). An immediate and sustained increase in urinary flow from preperfusion levels (0.3 ml/m^2/min) was noted, highest in the B-DRAT (3.8 ml/m^2/min), and less in the B-PT, patients (0.7 ml/m^2/min). However, glomerular filtration rate (GFR) fell to 45% of control. The fall in $T^c_{H_2O}$ was proportional to the fall in GFR.

It is concluded that the increase in urinary volume is solely attributable to excretion of "nonreabsorbable" solute (glucose and THAM), and occurs in the face of a marked diminution in GFR.

Left Ventricular Function and Tissue Anoxia in Irreversible Hemorrhagic and Endotoxin Shock (P)

Allan V. N. Goodyer, New Haven, Connecticut

Hemorrhagic shock in the dog becomes irreversible at a critical level of total-body oxygen debt (about 140 ml/kg). *Salmonella* endotoxin causes irreversible shock at a dosage of 5 mg/kg or more. In both circumstances, cardiac impairment can be detected preterminally, and has been invoked as a major cause of irreversibility. These experiments were designed to determine whether myocardial anoxia and/or ventricular failure are *necessary* conditions for irreversibility.

Anesthetized dogs were bled to a constant arterial pressure of 40 to 50 mm Hg, or given endotoxin intravenously (5 to 8 mg/kg). Ventricular function was evaluated by pressure-function curves during graded aortic obstruction and by pressure-rise velocity at standard afterload. Shock was monitored by repeated measurements of aortic pressure, cardiac output, oxygen consumption, and arterial "excess lactate" (X_L). Myocardial anoxia was evaluated by coronary sinus blood oxygen saturation and X_L concentration.

Left ventricular contractile capacity was well maintained, or even augmented (by increased sympathetic tone), when hemorrhage had led to irreversibility as judged by lethal oxygen debt and automatic retransfusion, or when endotoxin had led to respiratory arrest. Myocardial production of X_L was compatible with good ventricular contractile function, but production of lactate was associated with ventricular failure. Autonomic blockade impaired ventricular function, but did not uncover ventricular failure.

Although myocardial anoxia and ultimate failure occur during shock, ventricular contractile capacity is well maintained, partly by sympathetic support, even when irreversibility is established. Ventricular failure is not a necessary condition of irreversible shock.

Role of Sodium in Reactions to Contrast Media (P)

Norman L. Gootman, Abraham M. Rudolph, Emile M. Scarpelli, Nancy Buckley, and Michael Heymann, New York, New York

Elevations in left atrial and left ventricular end-diastolic pressures indicative of cardiac decompensation have been observed following the administration of angiographic agents to infants and children during cardiac catheterization. Possible mechanisms by which angiographic material may compromise cardiovascular function have been investigated in both the intact dog and the dog heart-lung preparation. The responses were studied to: (1) conventional angiographic agents containing 2,000 to 2,500 mOsm/L; (2) angiographic agents containing the same base but no Na; (3) hypertonic glucose; and (4) hypertonic Na solutions of equivalent osmolar concentrations.

Following injection of hyperosmolar NaCl or Na-containing angiographic agents into the aortic root or left ventricle, left ventricular end-diastolic,

left atrial, and pulmonary arterial pressures increased, and myocardial contractile force decreased. Injections of hypertonic glucose solutions or non-Na-containing angiographic agents produced minimal cardiovascular changes. The increase in total serum osmolality was similar following administration of each agent.

These studies indicate that hypertonic Na, administered as NaCl or in Na-containing angiographic media, compromises cardiac function. Additional experiments with the isolated perfused rabbit heart suggest, further, that hypertonic NaCl may produce these effects by promoting red blood cell agglutination in the coronary circulation.

Effect of Ouabain on Oxygen Consumption and Free Fatty Acid Oxidation in the Perfused Rabbit Heart

Aristides G. Gousios, James M. Felts, and Richard J. Havel, San Francisco, California

Rabbit hearts were perfused (10.0 ml/min) in a modified nonrecirculating Langendorff apparatus with a 20% suspension of bovine red cells (96 to 100% oxyhemoglobin) in bicarbonate buffer solution. The perfusate contained palmitate-1-C^{14} complexed to serum albumin (0.05% final concentration). Nine hearts served as controls. In six hearts, ouabain was infused at a constant rate through a side arm of the apparatus to give a final concentration of 2.8×10^{-7} M. The force of contraction, measured by a strain gauge attached to the left ventricle, increased in three to six minutes. Blood samples were collected from the cannulated pulmonary artery (venous) and from the reservoir just proximal to the heart (arterial) after 15, 25, and 35 minutes, and were analyzed for O_2 content and radioactivity in free fatty acids (FFA) and in CO_2. Ouabain produced no significant change in extraction of FFA, but increased FFA oxidation 70% ($P < 0.01$). In eight separate experiments, ouabain increased oxygen consumption from an average of 10.0 to 14.2 μmoles/min ($P < 0.01$). It is concluded that ouabain increases the O_2 consumption and force of contraction of the perfused rabbit heart; this is accompanied by increased oxidation of FFA.

Experimental Microvascular Suture Anastomosis (P)

George E. Green, Max L. Som, and William I. Wolff, New York, New York

The limits imposed by blood vessel size on success or failure of vascular anastomosis by suture techniques have not been completely defined. Few statistics have been published with respect to lasting patency after suture anastomosis of *arteries* less than 3 mm. No statistics on lasting patency after suture anastomosis of *veins* less than 3 mm have been published.

To evaluate these factors, tiny vessels in young CFN rats were anastomosed by microsuture technique, using the Zeiss operating microscope at 16 and 25 magnifications. In group I, aortas averaging 1.3-mm external diameter prior to manipulation were divided transversely and rejoined by suture anastomosis. In group II, inferior venae cavae averaging 2.7-mm external diameter prior to manipulation were similarly treated. In group III, both of these procedures were performed in each animal. There were ten animals in each group.

Of 40 consecutive anastomoses, only three were not patent when the animals were sacrificed three weeks after surgery. Two of the failures were arterial and one was venous. This high success rate was achieved only when certain refinements in technique had been perfected. The feasibility of suture anastomosis of extremely small veins, as well as arteries, has been demonstrated. Histological studies are in progress.

Evaluation of Estrogenic Substances in the Treatment of Cerebrovascular Disease (P)

Arnold H. Greenhouse, Albuquerque, New Mexico

Clinical investigations have indicated that estrogens are useful in the treatment of coronary atherosclerosis. A carefully controlled cooperative study of 560 men is in progress in 18 hospitals to determine the value of conjugated estrogens-equine in the prevention of recurrent cerebral infarction. Only patients with a definite diagnosis of atherosclerotic cerebral infarction were selected. They were randomly assigned to either estrogen or placebo medication in double-blind fashion. Treatment was begun in daily doses of 1.25 mg of conjugated estrogens, with an increase to 2.5 mg daily after the first year. Following institution of treatment, each patient was observed at two-month intervals for possible recurrence of cerebral ischemia, cerebral infarction, or other evidences of vascular occlusive disease. To date, 56 deaths have occurred, 31 among the 281 patients receiving estrogens and 25 among the control group of 279 patients. The cause of death was determined by careful evaluation of all available data, including autopsy examination when possible. Recurrent cerebral infarction was responsible for death in seven treatment and six control patients. Among the entire group, there were 56 recurrent cerebral infarctions, 33 in patients receiving estrogens and 23 in the control group. Reactions to estrogens appeared in approximately 10% (54 of 563) of the patients, usually consisting of breast tenderness

or enlargement. These preliminary observations indicate that estrogen therapy in the dosages employed has no beneficial effects on preventing recurrence of cerebral infarction or on fatality rates due to vascular disorders.

Effect of Reduced Coronary Flow on Myocardial Lactate Oxidation

Douglas M. Griggs, Jr., Shiro Nagano, Jose G. Lipana, and Paul Novack, Philadelphia, Pennsylvania

Essential to a better understanding of the physiological manifestations of coronary insufficiency is knowledge of the metabolic changes that occur in the intact myocardium during reduced coronary blood flow. A tracer method, based on the production of $C^{14}O_2$ from lactate-1-C^{14}, was devised for estimating the oxidation of blood lactate by the myocardium in the open-chest dog when blood flow to the cannulated left main coronary artery was at control or reduced rates.

Under control conditions, myocardial lactate oxidation in 11 dogs averaged 31.4 ± 10.9 μM/100 g/min, and closely approximated the net uptake value. Myocardial oxygen consumption attributable to lactate oxidation averaged 24% (94 μM/395 μM). When coronary flow was reduced to insufficiency levels in seven of these animals, as judged by a rise in left atrial pressure and S-T segment changes on the electrocardiogram, myocardial lactate oxidation persisted at 14.9 ± 0.05 μM/100 g/min, but the arterio–coronary sinus lactate difference revealed net myocardial lactate production. Pyruvate uptake and coronary sinus pH were reduced. The percentage of myocardial oxygen consumption attributable to lactate oxidation was not significantly different ($P > 0.2$); but when the effect of changes in the arterial lactate concentration were considered, it was apparent that the values obtained during reduced flow fell below those predicted from the control data.

The results are consistent with those of others, suggesting regional differences in aerobic versus anaerobic metabolism in the contracting myocardium, and/or a non-NAD–linked process for the dehydrogenation of lactate. Suppression of lactate oxidation by competing substrates during coronary insufficiency is suggested.

Natural History of Pulmonary Hypertension in Normal Adult Residents of High Altitude

Robert F. Grover, J. Thomas Okin, Hugh R. Overy, Denver, Colorado, Albert Treger, Chicago, Illinois, and Frank H. N. Spracklen, Denver, Colorado

At the moderate altitude of 10,200 feet (Leadville, Colorado), chronic hypoxia produces significant pulmonary hypertension in adolescents. To aid in understanding the natural history of this phenomenon, 217 adult residents of Leadville were examined clinically. From this group, approximately 30 normal adults in each decade were selected. From standard scalar electrocardiograms, the mean QRS axis (ĀQRS) was determined. ĀQRS was more rightward at all ages when compared with residents at sea level. However, just as seen at low altitude, ĀQRS shifted progressively to the left with increasing age.

To demonstrate the presence of pulmonary hypertension, implied by this right-axis deviation, 18 normal adults 26 to 57 years old were studied by cardiac catheterization in Leadville. At rest, the average mean pulmonary arterial pressure ($P_{\overline{PA}}$) was twice normal, being 28 mm Hg (range, 18 to 40). During exercise which increased oxygen uptake fourfold, average $P_{\overline{PA}}$ was 50 mm Hg (range, 30 to 60), and the range of systolic $P_{\overline{PA}}$ was 42 to 102 mm Hg. Relief of hypoxia by oxygen administration during exercise lowered $P_{\overline{PA}}$ an average of 10 mm Hg.

The severity of pulmonary hypertension was not clearly related to chronological age, age at which the adult moved to high altitude, or duration of residence at high altitude. A resting $P_{\overline{PA}}$ of 55/30 was found in a 37-year-old man after only eight months in Leadville, whereas a woman 41 years old had a $P_{\overline{PA}}$ of only 29/12 after living at high altitude since birth. Since $P_{\overline{PA}}$ in older adults is not higher than in adolescents, the hypertension does not appear to progress in severity with age.

Stimulation and Inhibition of Reparative Processes Following Myocardial Infarction

Sigmundur Gudbjarnason, John Fenton, and Richard J. Bing, Detroit, Michigan

Myocardial infarction was produced in dogs by ligation of branches of the anterior and posterior descending coronary arteries. The rate of incorporation of glycine-2-C^{14} into protein and nucleic acids was studied over a period of ten weeks. The reparative processes were stimulated with anabolic hormones and low-molecular substances known to accelerate wound healing. Insulin and growth hormone increased protein synthesis in infarcted tissue by 50 to 100%. Anabolic steroids stimulated incorporation into protein up to 500%. Treatment with ascorbic acid and glutathione increased protein synthesis of infarcted tissue three- to fourfold. Anabolic hormones also increased the synthesis of nucleic acids in the infarcted area. The earliest response to stimulation of the reparative processes was observed in synthesis of RNA from nucleolus and nucleoplasm. Animals fed on protein-deficient diets showed inhibition of the reparative processes, with

an early reduction in protein synthesis of mitochondria. Prolonged fasting or feeding on a protein-deficient diet resulted in the formation of thin scars (2 mm), and frequently led to development of aneurysm.

Role of Atelectasis in Pulmonary Surfactant Abnormalities Following Cardiopulmonary Bypass (P)

James L. Guest, Jr., Srboljub M. Sekulic, Thomas J. Yeh, Lois T. Ellison, and Robert G. Ellison, Augusta, Georgia

This study was carried out to determine the incidence of surfactant abnormality following cardiopulmonary bypass and to evaluate the relative importance of atelectasis compared with other factors thought to be responsible for postperfusion surfactant changes.

Lung biopsies were obtained in 32 patients during operation, one hour after completion of cardiopulmonary bypass (perfusion time, 32 to 218 minutes; mean, 116 minutes) performed for a variety of congenital and acquired lesions. In four other patients, postmortem lung samples were obtained 8 to 48 hours postoperatively. Surface tension, determined by the minced-lung technique with the Wilhelmy-Wilson balance and/or the Pattle bubble technique, was normal in 26 of these cases, including all four of the latter group. In dogs, surfactant was determined at intervals up to 24 hours following a variety of closed-chest bypass procedures. In one group, lung expansion was maintained by a respirator, and in another group respiration was spontaneous. Only 3 of 17 dogs in the lung-inflated group exhibited decreased surfactant, in contrast with five of nine dogs with spontaneous respiration.

Surfactant abnormalities were encountered consistently only in areas of localized edema or atelectasis. No correlation was observed between surfactant abnormality and perfusion time, hemolysis, hemodilution in the extracorporeal circuit, or blood gas analyses. The data suggest that postoperative atelectasis is a cause, rather than a result, of decreased surfactant; that abnormal results may be obtained in atelectatic areas if sufficient lung expansion is not carried out prior to sampling; and that this abnormal surfactant may not be related specifically to cardiopulmonary bypass.

Brain Stem Vagal Mechanisms Regulating Heart Rate (P)

Chesterfield G. Gunn, Gunnar Sevelius, Oklahoma City, Oklahoma, and Marcelo J. Puiggari, St. Louis, Missouri

Because the literature concerning the site of origin of vagal motor neurons which innervate the heart is confusing, a stereotaxic exploration of the brain stem in 28 chloralose-anesthetized cats was made using small bipolar concentric electrodes. Vagal nerve–evoked activity, blood pressure, right atrial cavitary electrocardiographic lead, and respiration were monitored. Criteria for a positive vagal cardiac mechanism included the presence of cervical vagal nerve–evoked potentials and slowing of the heart, with no change or a fall in the blood pressure during electrical stimulation. Consistently, electrical stimulation of an area either in or lateral to the nucleus ambiguus produced vagal nerve activity and slowing of the heart. In two animals, stimulation of the nucleus of the tractus solitarius produced this effect. In no instances did stimulation of the dorsal nucleus of the vagus produce any vagal nerve activity or slowing. When these experiments were repeated in 25 dogs to check species differences, the nucleus ambiguus remained most important to the origination of vagal cardiac inhibition. The nucleus of tractus solitarius occasionally activated cardiac vagus fibers, and in some instances the dorsal nucleus of the vagus can also activate vagal fibers to the dog's heart. Central and peripheral vagal mechanisms can inhibit conduction in both the atrium and the ventricle. Under certain conditions, stimulus-bound arrhythmias, including atrial fibrillation, occurred with vagal activation. The ambiguus area, therefore, shows a dominant and previously unrecognized role in vagal control of the hearts of both cat and dog.

Acute Hemodynamic Effects of Methoxamine and Norepinephrine in Myocardial Infarction With and Without Shock (P)

Rolf M. Gunnar, Antonio Cruz, Jeb Boswell, Bun Siu Co, Raymond J. Pietras, and John R. Tobin, Jr., Chicago, Illinois

The acute hemodynamic effects of myocardial infarction were measured in 18 patients, and the effects of two pressor amines were studied in eight. Aortic and superior vena caval pressures were measured through polyethylene catheters. Cardiac outputs were estimated by the indicator-dilution method.

I. *Myocardial infarction without shock–11 patients.* The average cardiac output (CO) was 3.8 (1.7 to 6.9) L/min; mean arterial pressure (MAP) was 92 (64 to 140) mm Hg; and total peripheral resistance (TPR) was 26 (16 to 52) mm Hg/L/min. Two of these patients were given norepinephrine, and both showed a rise in mean arterial pressure with a fall in cardiac output.

II. *Myocardial infarction with shock–seven patients.* Control studies showed an average CO of 1.9 (0.6 to 2.6) L/min; MAP of 50 (30 to 60) mm Hg; and TPR of 33 (16 to 113) mm Hg/L/

min. Three patients received methoxamine, resulting in a decrease in CO which averaged 19% (16% to 21%). The MAP did not change in one and increased 11% and 21% in the other two. TPR decreased 16% in one and increased 218% and 100% in two. Six patients received norepinephrine, resulting in an average increase in CO of 33% (12% to 57%), and an increase in MAP of 74% (3% to 175%). The TPR decreased 5% and 19% in two, and increased 87% to 106% in the others.

These studies suggest that a vasopressor agent with both inotropic and vasoconstrictor effects (norepinephrine) exerts a salutary effect (increase in flow and blood pressure) on patients in shock from myocardial infarction. This is unlike the effects in patients not in shock or hypovolemic shock. A pure vasoconstrictor agent decreases flow in the same patients.

Supernormal Character of the Strong Beat in Pulsus Alternans

Warren G. Guntheroth, Beverly C. Morgan, John P. Lintermans, George A. McGough, and Melvin M. Figley, Seattle, Washington

Pulsus alternans occurred spontaneously in a healthy dog. Ultrasonic flow probes had been implanted on the aorta and pulmonary artery three weeks previously. Inadequate diastolic filling did not appear to be an adequate explanation for pulsus alternans. There was frequently an inverse relationship between the end-diastolic pressure of the right ventricle and the succeeding pulse amplitude in the pulmonary artery. Although there was a direct relationship between left ventricular end-diastolic pressure and aortic pulse amplitude, the relationship was nonlinear, reflected in marked fluctuations in pulse amplitude with small variations in end-diastolic pressure. The same nonlinear relationship held for diastolic volumes (determined by angiocardiography) preceding the weak and the strong beats. Particularly striking was the *initiation* of pulsus alternans with a supernormal beat, which is incompatible with the theory of inadequate ventricular filling.

The supernormal character of the strong beat of the pair in pulsus alternans was repeatedly demonstrated. As alternans developed, there was a distinct, double "staircase effect," with a progressive decline in pulse amplitude of half the beats, and a progressive increase in amplitude of the alternate contractions. The potentiation of half the beats in pulsus alternans may involve a mechanism similar to postextrasystolic potentiation, or the potentiation produced by driving the heart with closely spaced, paired stimuli: the force of contraction lost in the weak beat appears in the strong beat. In short, pulsus alternans may better be regarded as a coupling of weak and supernormal beats rather than weak and normal contractions.

Pulmonary Emboli Recurring After Ligation of the Inferior Vena Cava (P)

Victor Gurewich and Duncan P. Thomas, Boston, Massachusetts

Eight cases of recurrent pulmonary emboli occurring from ten days to four years following inferior vena cava (IVC) ligation have been encountered during the past two years. Diagnosis of recurrent emboli was based on a characteristic clinical picture in all cases, confirmatory roentgenographic observations on plain film or pulmonary angiograms in seven patients, electrocardiographic evidence of acute cor pulmonale in five subjects, and elevated LDH with normal SGOT in all but one. Venagrams were obtained in five patients, and large collateral channels were demonstrated in each case. These collateral veins, which may approximate the IVC in caliber, were found to develop within four months of the ligation.

These observations indicate that IVC ligation may be only temporarily effective in protecting against pulmonary emboli. It is likely, since initial symptomatic improvement occurred following operation, that the emboli in these patients originated below the ligation site. Subsequent development of large collateral channels permitted thrombi formed in the areas of retarded venous flow to reach the lungs. If venous thromboembolic disease develops as a result of stasis and hypercoagulability, as has been suggested, then it follows that vein ligation, unlike anticoagulant therapy, tends to compound one abnormality without correcting the other. Although IVC ligation can be performed with a low operative mortality and morbidity, it should not be considered the treatment of choice in venous thromboembolism, and should be reserved for patients in whom anticoagulant therapy has either failed or cannot be employed.

A Classification of Congenital and Acquired Heart Disease Designed for Use with Data-Processing Systems

Alvin Hackel, John J. Osborn, and Frank L. Gerbode, San Francisco, California

A classification of congential and acquired heart disease designed specifically for use with data-processing systems has been developed. This classification was devised because of the need for a diagnostic code in a form suitable for use with computer programs, and is an attempt to bring together existing classifications of congenital and acquired heart disease of a descriptive anatomical

type, including new information in this field. It is being used in digital and concept-coordination data-processing systems to correlate cardiac diagnoses at various levels of diagnostic and therapeutic procedures. It is hoped that this classification will provide a common language of cardiac lesions for cardiologists, cardiovascular surgeons, pathologists, and anatomists.

The classification consists of a series of terms, each term being a specific anatomical lesion. There are no complexes or combinations of lesions listed under a single term. This method allows analysis of the frequency of lesions either individually or in combination with other lesions and gives more flexibility to a data-analysis system. In addition, the form of the classification allows revision and addition without significant change in the construction of the code.

Potential Pacemaker Activity in the Left Atrium in Early Stages of Development of the Chick Embryo

Gershon Hait, New York, New York, and Richard Licata, Chicago, Illinois

Simultaneous left and right atrial surface electrograms from 30 chick embryos were obtained at three different stages of development: group I, 6 to 7 days; group II, 10 to 11 days; and group III, 15 to 16 days of incubation. Serial electrograms were obtained from 1 to 56 minutes after the removal of the embryo from the egg. Circulation was intact and the temperature was maintained constant.

Analysis of the P waves demonstrated two components which could be detected as right and left atrial depolarization and which were separated by an average of 7 msec in the early tracings and 16 msec in the late tracings. In all the older embryos (groups II and III), the first component of the P wave was the result of right atrial depolarization. The same order of depolarization was observed in group I in the four hearts in the most advanced stage of development in this group. In the four hearts of this group in the least advanced stage of development, left atrial depolarization preceded right atrial depolarization. In two additional embryos in group I, the initial depolarization was from the right atrium during the first ten minutes of observation, and reverted to an initial left depolarization 4 to 12 minutes later.

These observations show that during the early stages of development, at or before six to seven days, left atrial depolarization precedes right atrial depolarization, suggesting the presence of potential pacemaker activity in the left atrium. At this stage of development, a left sinoatrial node is a likely supposition.

Postexercise Plasma and Urinary Norepinephrine and Epinephrine Levels Among High Social Class and Low Social Class Males and Subjects with Nonacute Coronary Heart Disease in Evans County, Georgia

Curtis G. Hames, Claxton, Georgia, Marshall A. Lichtman, Chapel Hill, North Carolina, and John R. McDonough, Washington, District of Columbia

An epidemiological study of cardiovascular morbidity in Evans County, Georgia, has found an elevated prevalence of coronary heart disease (CHD) among high social class (HSC) as compared with low social class (LSC) males, independent of cholesterol level, blood pressure level, and race. The following studies were undertaken to examine possible differences in adrenergic nervous system function in groups previously shown to have a high (HSC males) and low (LSC males) prevalence of CHD. Daily urinary norepinephrine (NE) and epinephrine (E) excretion was assessed in a random sample of 61 HSC and LSC subjects. Urinary E excretion was similar, whereas NE excretion was 83% greater in HSC than in LSC men ($P < 0.001$). This difference persisted after adjustment for differences in creatinine excretion and body size. Eighty-four per cent (21 of 25) of HSC men, compared with 25% (9 of 36) of LSC men had a daily NE excretion in excess of 76 μg ($X^2 = 18.3$, $P < 0.001$). Postexercise plasma (PEP) catecholamine levels measured in a second random sample of male subjects revealed a 47% higher NE level in HSC than in LSC males ($P = 0.07$); PEP E levels were similar. Seventy-one per cent (10 of 14) of HSC, compared with 35% (7 of 20) of LSC, males had PEP NE levels above 4.10 μg/L ($X^2 = 3.04$, $P = 0.08$). The replication of elevated NE levels and similar E levels in HSC, compared with LSC, males in two different samples is mutually confirmatory. An association of social-class index with both PEP NE ($r = 0.42$, $P < 0.02$) and urinary NE ($r = 0.54$, $P < 0.01$) was found. Studies of males with nonacute CHD revealed an E excretion similar to that in HSC and LSC males; however, NE excretion was greater than in either HSC or LSC men ($P < 0.001$). These preliminary data suggest an association of social class, NE metabolism, and CHD.

Factor Analysis of QRS from Varied Cardiac Generators

Robert L. Hamlin, Earl M. Raley, Clinton R. Foulk, and C. R. Smith, Columbus, Ohio

Unipolar electrocardiograms were recorded simultaneously with orthogonal electrocardiograms

from 18 points on the thorax of healthy dogs and goats, dogs with left and right ventricular pacemakers, dogs with right ventricular hypertrophy, and from the "combined thorax" of two dogs "pasted" together with electrode jelly and with contralateral ventricles paced simultaneously. Factor analysis of the electrocardiograms was performed to estimate the percentage of the total electrocardiographic information that might be obtained from three factors extracted from all 18 electrocardiograms.

Three factors represented over 97% of the information in animals from all groups, except those comprised of the two dogs "pasted" together; in this group, seven factors were required, since three factors provided only 70% of the information. In configuration, each of the three factors had a coefficient of correlation greater than 0.97 with one of the commonly used orthogonal electrocardiograms.

"Single" hearts with widely differing pathways of ventricular depolarization may be represented as a three-function generator; but "one animal" containing two simultaneously paced hearts may not be represented as a three-function generator. The former group may be dipolar—the latter group must not be dipolar.

Operative Treatment of Multiple Sites of Extracranial Artery Occlusion (P)

Creighton A. Hardin, Kansas City, Kansas

It is our belief that all compromised extracranial obstructed arteries should be restored at the time of initial surgery. The Seldinger technique of aortography was used to demonstrate accurately the sites of arterial blockade. One hundred and five patients have had two or more major extracranial systems surgically corrected. The restoration of all sites of arterial obstruction should increase the effectiveness and efficiency of cerebral arterial blood flow.

Thirty-one patients had both vertebral arteries obstructed; the causes of arterial block were intraluminal plaque, redundancy or kinking, extraluminal fascial bands, and spondylosis of the bony vertebral canal. Thirteen patients had one carotid and one vertebral artery simultaneously repaired. Thirty-six patients had bilateral carotid occlusion corrected. Twenty-two patients had two carotid arteries, a vertebral, subclavian, or innominate block. Thirteen patients had subclavian, innominate, vertebral arterial occlusion. One hundred and fifty-nine patients have been operated on with only a single extracranial occluded artery involved.

These patients have been followed from 12 to 84 months. The follow-up has consisted of postoperative arteriography and neurological examination. Patients have been studied for residual symptoms after surgical correction. Paralytic and speech disturbance symptoms have been reverted in 88%; attitude, gait, and nystagmus in 90%; and blurred vision and diplopia in 90% of patients. Less frequently occurring neurological postoperative symptoms were also documented.

Measurement of Regional Coronary Blood Flow in the Intact Subject (P)

Maureen A. Harman, Angel K. Markov, Patrick H. Lehan, Henry A. Oldewurtel, and Timothy J. Regan,† Jersey City, New Jersey

Current methods for measuring coronary blood flow (CBF) in the intact subject fail to detect and localize regional differences in CBF. In an effort to detect such changes in regional flow, precordial decay curves of Kr^{85} injected rapidly at various levels of the coronary sinus (CS) were studied in 27 intact dogs. Tissue counts from localized areas of myocardium following rapid injections of radioisotope into the CS indicate that the temporary increase in pressure resulting from injection allows retrograde diffusion of gas into selected areas of the myocardium. A comparative study of 110 precordial decay curves obtained sequentially following the injection of Kr^{85} into the circumflex branch of the left coronary artery and the CS showed good agreement ($r = 0.88$) at a mean flow level of 97 ml/100 g LV/min. Regional changes in CBF were produced by gradual induction of a thrombus in the left anterior descending artery (LAD). Comparison of 146 precordial curves obtained by injecting Kr^{85} into the coronary artery distal to the thrombus and injection into the anterior great cardiac vein indicate that at the latter site of injection, regional areas of flow could be accurately detected down to a level of 9 ml/100 g LV/min ($r = 0.90$). Withdrawal of the catheter to the proximal CS position permitted the discrimination of normal flow areas (circumflex) from low flow areas (LAD). No changes in electrocardiogram, hemodynamics, or coronary inflow were elicited by injection into the CS. It is concluded that CS injection of Kr^{85} provides a safe and sensitive index of regional CBF.

Factors Influencing Electrocardiographic Changes at High Altitude

Charles W. Harris and James E. Hansen, Denver, Colorado

The significance of electrocardiographic changes during high-altitude exposure is disputed, and the relative contributions of altitude change, speed of ascent, length of stay, exercise conditions, and,

especially, ventilatory variations on the ECG changes are uncertain. Serial ECG's were taken on 42 healthy young men living at sea level (22 men) or in Denver (20 men—altitude 5,280 feet) and during a four- or five-week residence at 11,400 or 14,110 feet. The relationship of the following variables to the observed ECG changes was determined: (a) altitude change; (b) speed of ascent; (c) length of stay; (d) strenuous daily exercise; (e) inspiratory volume; and (f) heart and pulmonary artery size (by X-ray).

Variance analyses reveal significant ($P = < 0.01$) progressive rightward-posterior QRS-axis shifts and significant ($P = < 0.05$) temporary heart rate increases, QRS-amplitude decreases, and right precordial T-wave inversions in all groups at altitude, except in the Denver subjects at 11,400 feet. The QRS-axis shifts persisted for at least ten days after return to sea level from 14,110 feet. The pulmonary artery, but not the heart size, increased ($P = < 0.05$) in the sea-level subjects at 14,110 feet. The variables of altitude change, length of stay, and pulmonary artery size significantly ($P = < 0.05$) influenced ECG changes at altitude; however, daily exercise, speed of ascent, and maximum inspiration had no effect ($P = > 0.1$). The temporary QRS-amplitude and T-wave changes suggest a direct cardiac effect of hypoxia, while the progressive and prolonged QRS-axis shifts appear related to changes in pulmonary perfusion rather than ventilation.

Beta Component in Circulatory Actions of Norepinephrine in Man

Willard S. Harris, Clyde D. Schoenfeld, Arnold M. Weissler, and Richard H. Brooks, Columbus, Ohio

Norepinephrine has been found to have potent beta or cardiostimulatory activity in isolated hearts and (by strain-gauge studies) in anesthetized man. Yet, in intact man, its circulatory effects appear to result mainly, perhaps entirely, from vasoconstriction due to its α-receptor activity. The possible contribution of β-activity to the hemodynamic responses to norepinephrine was studied during cardiac catheterization by comparing these responses in 12 normal subjects before and after β-receptor blockade by intravenous propranolol (10 mg).

Norepinephrine (15 μg/min) produced identical elevations (+28 mm Hg) of mean arterial pressure before and after β-blockade. *Before* β-blockade, cardiac index (CI) fell 14% (−0.41 L/min/m^2), while heart rate (HR) decreased 18 beats/min and stroke volume (SV) rose 16 ml. *After* β-blockade, the same dose of norepinephrine resulted in a significantly greater fall ($P < 0.005$) of CI (−0.91 L/min/m^2, −32%), while HR decreased 20 beats/min and SV fell 2 ml. β-blockade similarly altered the responses to 7.5 μg/min and 22.5 μg/min of norepinephrine. β-blockade failed to influence the decrease of CI, HR, and SV accompanying graded elevations of peripheral resistance produced by methoxamine (five subjects) and angiotensin (six subjects), agents which lack β-adrenergic activity.

In intact man, norepinephrine acts to help preserve cardiac output by β-stimulation at the same time that it raises peripheral resistance by α-activation. The results also indicate that elevation of peripheral resistance does not increase endogenous cardiac β-adrenergic activity.

Evidence for Multiple Circulatory and Metabolic Beta-Receptors in Man

Willard S. Harris, Clyde D. Schoenfeld, Arnold M. Weissler, Richard H. Brooks, and James V. Warren, Columbus, Ohio

Do adrenergic actions which are inhibited by β-blocking agents have identical receptor mechanisms? To answer this question, we have compared the responses of normal human subjects to isoproterenol (2.5 μg/min) and epinephrine (5.0 μg/min) before and after β-adrenergic blockade.

In 30 subjects, isoproterenol increased cardiac index (CI) 68% (+2.20 L/min/m^2) and heart rate (HR) 40% (+28 beats/min). In ten subjects, epinephrine increased CI 46% (+1.48 L/min/m^2) and HR 19% (+13 beats/min). After β-receptor blockade by propranolol, isoproterenol had no effect, but epinephrine, due to its unopposed α-vasoconstriction, decreased CI 25% and HR 21% and raised total peripheral resistance 53%. Isoproterenol (five subjects) increased oxygen consumption 27% and arterial free fatty acids (FFA) +448 μEq/L, lactate +0.18 mM/L, and glucose +5 mg/100 ml. Epinephrine (six subjects) increased oxygen consumption 25%, FFA +1,000 μEq/L, lactate +1.06 mM/L, and glucose +44 mg/100 ml. Except for epinephrine-induced glucose mobilization, propranolol blocked all metabolic effects of both agents.

Although at these dose levels both agents caused comparable cardiac stimulation and virtually identical elevations of oxygen consumption, epinephrine far exceeded isoproterenol in its effects on FFA and lactate. The disparity of these responses to two activating agents is not well explained by a simple α-β-receptor hypothesis. The present observations are more consistent with the existence of multiple adrenergic receptors, several of which are blocked by propranolol.

Fiberoptics for In Vivo Monitoring of Oxygen Saturation and Hemodynamics

Donald C. Harrison, Narinder S. Kapany, Harry A. Miller, Norman Silbertrust, and Rogers P. Drake, Palo Alto, California

In recent years, a considerable interest has been shown in the use of fiberoptics catheters for determination of oxygen saturation and dye concentration by remote spectrophotometry. Further investigations in these laboratories have suggested the extension of these techniques for continuous venous and arterial monitoring of oxygen saturation. In eight studies utilizing dogs breathing various oxygen mixtures, these fiberoptics techniques have been used for continuously monitoring arterial and venous oxygen saturation, and the results have been compared with in vitro oxygen saturation determinations by reflection and transmission oximetry. A high degree of correlation between in vivo and in vitro measurements has been achieved with oxygen saturations ranging from 48 to 100%.

In addition, detailed spectrogoniophotometric studies of blood under dynamic flow conditions have been made. Polar plots of light scattered by the red cells have shown that accurate oxygen saturation can be determined during wide variations of flow, temperature, and hematocrit. These techniques also appear to have significant potential for the determination of changes of in vivo hemodynamics.

Calcification of the Left Atrium: Its Significance, Detection, and Proposed Surgical Management

J. Warren Harthorne, Ronald A. Selzer, and W. Gerald Austen, Boston, Massachusetts

The natural history of calcification of the left atrium is that of chronic, long-standing rheumatic heart disease, usually associated with atrial fibrillation, multivalvular lesions, and systemic embolism. Mitral valvular surgery in such patients is difficult, if not impossible, and is complicated by difficulty in entering the left atrium, left atrial thrombi, and impaired hemostasis. Detection is best made by image-intensification fluoroscopy. Fifteen cases observed during the past six years are added to the 62 reported in the literature. The diagnosis was confirmed by surgery and/or postmortem examination in 12 cases and by X-ray alone in three cases. There were 13 females and two males. Three patients had "pure" mitral stenosis, while 12 had mixed lesions. Surgery was frequently complicated, as indicated above. Sixteen operations were performed in ten patients, with four operative deaths (25%). A review of the surgical and pathology literature and experience with the present series reveals that the atrial septum may be spared in the process of calcification and provides easy access to the mitral valve in such cases. It is concluded that:

1. All patients considered for mitral valvular surgery should be carefully screened for intracardiac calcification by image-intensification fluoroscopy or other appropriate techniques.
2. Closed mitral valvulotomy through a standard left thoracotomy is hazardous in such patients because of the risk of embolism, hemorrhage, and difficulty in entering the left atrium.
3. Open valvuloplasty, utilizing cardiopulmonary bypass, right thoracotomy, and approach to the mitral valve through the atrial septum or posterior interatrial groove, offers significant advantages.

Spectrum of Artificial Valve Heart Sounds

W. Proctor Harvey, Antonio C. de Leon, Jr., and Charles A. Hufnagel, Washington, District of Columbia

Auscultatory and phonocardiographic features of 50 patients with various prosthetic valves were studied (Hufnagel mitral and aortic disc, aortic leaflets, ball valve, and Starr-Edwards ball valve prostheses).

Aortic valve opening corresponded to the timing of the usual aortic ejection sound. The opening sound may be mistaken for the first heart sound. All had systolic murmurs (grade 1/6 to 3/6), and one-third had a diastolic blow (grade 1/6 to 3/6).

Thoracic aorta ball valve: The first heart sound is usually easily heard. The sound of valve opening is late (0.19 second from Q of the electrocardiogram) and, hence, is heard during the early part of the systolic ejection murmur. The sound of valve closure is accordingly late, heard in early diastole.

Mitral valve: Mitral valve closure produces a loud sharp sound. It opens 0.09 to 0.13 (average, 0.10) second after the sound of aortic closure, and represents an "opening snap." Occasionally a faint diastolic rumble is present.

Atrial and ventricular diastolic gallops were noted frequently with aortic prostheses, but were conspicuously absent with a mitral prosthesis. The ball valve produced the loudest sounds and widest transmission. The aortic leaflets best simulated the normal sounds. Disc valve sounds were of intermediate intensity.

Unusual auscultatory features have been encountered. The aortic valve prosthesis may produce systolic clicks. Occasionally, the ball valve may roll within its cage, producing multiple systolic sounds, sometimes suggesting clots. The mitral prosthesis may produce a double closure sound or a midsystolic click. An intermittent

pansystolic murmur may occur with incomplete closure of the valve.

The increasing number of patients with artificial valve prostheses makes awareness of their auscultatory features important.

Pitfalls in Diagnosis of Primary Myocardial Disease (P)

W. Proctor Harvey, Jack P. Segal, and T. James Waters, Washington, District of Columbia

In 385 patients with primary myocardial disease, the most difficult diagnosis was that of distinguishing between this condition and arteriosclerotic heart disease. In the male over 40 years, coronary disease should be suspected whenever there is a history of hypertension, diabetes, hypercholesterolemia, or gout. A classical infarction pattern and coronary insufficiency pain are strong (although not definite) evidence for arteriosclerotic heart disease. Extreme cardiomegaly favors primary myocardial disease. It may mimic hypertensive, valvular, congenital, and pulmonary hypertensive heart disease. Those patients with cardiac decompensation and cardiomegaly frequently have both atrial and ventricular diastolic gallops, elevation of blood pressure, and murmurs of mitral and tricuspid insufficiency; with compensation, these return toward normal. In contrast, with hypertensive heart disease, the pressure elevation persists, and with organic valvular disease the murmurs usually increase in intensity. Both pericardial effusion and primary myocardial disease may have cardiomegaly, feeble pulsations, and advanced cardiac decompensation; definite diagnosis may depend on angiographic techniques or pericardial tap. Constrictive pericarditis may simulate the restrictive type of primary myocardial disease. Arrhythmias (except atrial fibrillation) and advanced cardiac enlargement favor primary myocardial disease, although the diagnosis is sometimes resolved only by surgical exploration. Embolic complications may be mistaken for pneumonia, aortic dissection, brain tumor, and stroke. Less confusion exists with the congenital group, but include Ebstein's anomaly and even atrial defect. Aortic insufficiency is rare. The combination of a normal electrocardiogram and X-ray almost excludes the diagnosis of primary myocardial disease.

Long-Term Hemodynamic Data in Postoperative Patients with Transposition of the Great Vessels (P)

Alois R. Hastreiter, Maria Serratto, Federico R. Arevalo, and Robert A. Miller, Chicago, Illinois

Twelve patients were studied who had transposition of the great vessels partially corrected by the Baffes procedure. A mean interval of 5.8 years had elapsed from the time of surgery. All were attending regular school, with varying amounts of restriction on activity; two required digitalis.

The systemic oxygen saturation in nine of the 12 patients ranged from 82 to 94% (mean, 88%); the lowest systemic saturation (76%) occurred in a patient in whom the graft from vena cava to left atrium was occluded. In one patient with an additional left-to-right shunt due to anomalous drainage of the left upper lobe pulmonary vein into the superior cava, the pulmonary arterial saturation was lower than systemic. The pulmonary flow was higher than systemic in four cases (2 to 4:1) and about equal to it in the others. Prior to surgery, all patients had enlarged hearts and catheterization or X-ray evidence of increased pulmonary blood flow. None at that time had pulmonary stenosis significant enough for a shunting procedure to be considered. Only two of the 12 patients now have marked pulmonary vascular obstruction; one has a large ventricular septal defect and the other a patent ductus with a small ventricular septal defect probably undergoing spontaneous closure.

Some obstruction to left ventricular flow was present in six cases. In two, the main pulmonary artery was entered and a significant gradient was found. In three other cases, pulmonary stenosis was visualized by the ciné method. The sixth case had distal obstruction caused by multiple coarctations of the branches of the pulmonary artery.

In three cases, normal left ventricular and pulmonary arterial pressures were found, one with a patent ductus only and the other two with ventricular septal defects. In the remaining case, moderate elevation of pulmonary arterial resistance was present.

Hemodynamics of Severe Aortic Insufficiency in Man

Richard R. Hawley, William A. Baxley, Harold Sandler, and Harold T. Dodge, Seattle, Washington

Left ventricular (LV) pressure-volume (P-V) characteristics were determined in two patients with severe aortic insufficiency (AI) and LV failure in whom aortic and LV diastolic pressures equilibrated at ventricular rates below 85/min. LV volumes were calculated from biplane angiocardiograms taken at 6/sec and from single-plane (anteroposterior) cineangiocardiograms at 30/sec, and timed with simultaneously recorded electrocardiograms and LV pressure. Volumes were calculated from cineangiocardiograms, assuming an ellipsoid of revolution reference figure, and ad-

justed for X-ray distortion and inequality of transverse diameters by factors derived from volumes calculated from the biplane angiocardiograms.

LV stroke volumes were 250 and 175 ml/beat and regurgitant flows 190 and 115 ml/beat, respectively. LV P-V curves demonstrated loss of isometric contraction and relaxation periods. LV compliance in early diastole was high, since volume changes greater than 150 ml occurred with little increase of pressure. Maximum LV diastolic pressure and volume occurred at the onset of equilibration of aortic and LV pressures (0.40 and 0.46 second of diastole, respectively), and LV pressure and volume decreased with longer periods of diastole. Stroke work values calculated from the P-V curve in one patient were: systolic work (334 g-m), three times normal; and work expended in distending the diastolic LV (35 g-m), seven times normal. LV pressure and volume decreased during the latter portion of diastole, representing work performed by the diastolic LV from energy stored earlier in diastole.

These studies demonstrate the use of a quantitative cineangiocardiographic method to define hemodynamic features of severe AI.

Effects of Isoproterenol, Ephedrine, and Potassium on Artificial Pacemaker Failure

Julian Haywood, Los Angeles, California, and Milford G. Wyman, San Pedro, California

Despite advances in material usage, design, and battery capabilities, failure of implanted artificial pacemakers is not an infrequent occurrence, and patients again become subject to the hazards of Stokes-Adams attacks. Failure may occur where optimal care is not immediately available to the patient. Studies have been made of three patients to determine the effect of medical therapy on pacemaker failure.

Oral sublingual isoproterenol was shown to cause resumption of pacemaker function in all three patients, lasting variable periods of time. One patient was studied in detail. Oral sublingual isoproterenol, 15 mg, was given on several occasions, with resulting full resumption of pacemaker function lasting from 45 minutes to two hours; on other occasions, an increase in the idioventricular rate alone occurred. Oral ephedrine, 25 mg, mimicked the latter effect of isoproterenol. Intravenous isoproterenol in a concentration of 1 mg/100 cc resulted in full pacemaker function within two minutes; this effect was lost within five minutes of stopping the drip. This effect was repeated several times. Mild side effects were noted. Oral potassium (40 mEq in a single dose) and intravenous potassium (20 mEq/200 cc) on several separate occasions resulted in intermittent pacemaker function and coupled rhythm due to premature beats occurring in the supernormal phase.

No deleterious effects of either therapy were noted; however, sublingual or intravenous isoproterenol is the emergency drug therapy of choice when catheter pacing cannot be immediately instituted.

Methods for Angiocardiodensitography: A New Indicator Technique

Paul H. Heintzen and Joachim H. Bürsch, Kiel, Germany

The radiopaque material injected during angiocardiography was used as indicator, and the changes of X-ray density of the different heart chambers and vessels were measured during the passage of the contrast medium (Urographin 76%). The following methods for the recording of radiopaque dilution curves have been developed.

A. *Cineangiocardiodensitography.* Silicium photocells of different size and shape were placed within the cone of light of a projected cineangiocardiogram (60 to 80 frames/sec) and densitograms were recorded by means of a direct-recording system (normally used in dye-dilution studies) or via d-c amplifiers and commercial electrocardiographic recorders. A rotating sector disc periodically interrupted the X-ray radiation and acted as a real-time marker; it allowed the measurement of local circulation times (appearance, buildup, disappearance, and recirculation times). In addition, the time marker is used for the synchronization of the densitograms with any reference tracing recorded during angiocardiography.

B. *Fluoroangiocardiodensitography.* A special photomultiplier including two light sources was adapted to the screen of an image intensifier. The light marks appearing on the television monitor indicate the exact localization of the photomultiplier. In contrast with cineangio- and videodensitography, the radiopaque dilution curves recorded during continuous X-ray radiation make it possible to detect very rapid density changes and to synchronize them exactly with any reference tracing picked up during angiocardiography.

C. *A twin photomultiplier* has been developed and used for the measurement of blood flow velocity within large and smaller pulmonic and systemic vessels during continuous X-ray radiation.

Active Physical Reconditioning of Coronary Patients (P)

Herman K. Hellerstein, Alfredo Burlando, Eugene Z. Hirsch, Franklin H. Plotkin, George H. Feil, Oliver Winkler, Sue Marik, and Neil Margolis, Cleveland, Ohio

The effects of a program of supervised, graded, individualized exercise (up to 400 Calories/hour,

three to five times weekly) were evaluated in 53 men with coronary artery disease. Thirty-nine had myocardial infarcts and 14 angina pectoris; none had congestive heart failure. All subjects were prescribed a restricted caloric and cholesterol diet.

The mean age was 48.8 years, range 33 to 62 years. Evaluation included history, physical examination, psychological tests, electrocardiograms, serum cholesterols, and multilevel steady-state bicycle ergometer exercise tests. The group was subdivided into group A (38 subjects, full adherence to program), group B (9, partial adherence), and group C (6, nonadherence). Follow-up to date totals 84.8 patient years, with an average of 19.0 months per individual. There have been two deaths, one in group A and one in group B.

Over-all objective improvement (in exercise ischemic S-T displacement, heart rate, blood pressure, systolic tension-time index) occurred in 69.8% of the total group, and varied with adherence: 81.6% group A (31/38); 5/9 B; and 1/6 C; 20.8% showed no change and 9.4% deteriorated. Initial test ischemic S-T displacement, occurring in 24 subjects (17 A, 4 B, 3 C), subsided after training in 54% (13 subjects)—70.6% A, 25% B, and none C. After training, group A differed from groups B and C insignificantly in weight loss (1.8 kg, 0.5 kg), but significantly in reduction of cholesterol ($P < 0.005$) and systolic tension-time index ($P < 0.001$ versus $P > 0.4$). The physical work load necessary to produce a heart rate of 150 increased significantly in adherents, from 7.89 to 10.00 kpm/min/kg body weight ($P < 0.001$), and insignificantly in nonadherents ($0.2 > P > 0.1$). Active physical reconditioning has therapeutic merit for selected patients with coronary arterial disease.

Abnormalities in Lipid Formation by Platelets from Young Patients with Myocardial Infarction (P)

Allen R. Hennes, Detroit, Michigan, Kozi Awai, Okayama, Japan, Jean C. Jackson, and Maxine L. Adams, Detroit, Michigan

We have studied in vitro incorporation of acetate-1-C^{14} into lipids by platelets from eight patients aged 34 to 52 years with myocardial infarction. All were studied two months to seven years postinfarction. None had received anticoagulants. Only one had diabetes.

Incorporation of C^{14} into fatty acids was decreased (12 controls = 36,310 ± 12,469 dpm/10^9 platelets; eight patients = 22,104 ± 14,638 dpm/10^9 platelets; $P < 0.05$). Gas chromatography of the fatty acids showed a decreased percentage of fatty acid–C^{14} in palmitate (controls = 27.4 ± 5.6; patients = 19.3 ± 4.4; $P < 0.01$). The percentage of C^{14} in oleate was increased (controls, 1.03 ± 0.33; patients, 7.63 ± 5.7; $P < 0.001$).

Silicic acid column chromatography of lipids revealed other abnormalities. The percentage of C^{14} in sterol ester fatty acids was increased (six controls = 1.48 ± 1.03; eight patients = 7.86 ± 1.28; $P < 0.01$), while the percentage of C^{14} in glyceride fatty acids was decreased (controls = 19.7 ± 2.3; patients = 10.26 ± 0.98; $P < 0.02$). The percentage of C^{14} in phospholipid fatty acids was increased, but not significantly; however, the pattern of phospholipid fatty acid–C^{14} was abnormal. The percentage of C^{14} in stearate was decreased (six controls = 22.3 ± 1.8; six patients = 10 ± 1; $P < 0.001$), while the percentage of C^{14} in fatty acids with retention time corresponding to 22:0 or greater was markedly increased (controls, 19.3 ± 3.37; patients, 46.2 ± 2.07; $P < 0.01$).

Lipid formation by platelets from relatively young patients with myocardial infarction may be abnormal. It is possible that such abnormalities could be related to the development of myocardial infarction.

Electrocardiographic, Metabolic, and Anatomic Predictions of Zonal Myocardial Ischemia in Coronary Artery Disease (P)

Michael V. Herman, Michael D. Klein, William C. Elliott, and Richard Gorlin, Boston, Massachusetts

To define the value of the standard 12-lead rest and exercise electrocardiogram in the quantitative evaluation of coronary artery disease, a study was made comparing such ECG's with selective cine coronary angiography and catecholamine-induced myocardial lactate production. Zones of myocardial ischemia (ZI) were distinguished on the ECG by a locus of old infarction or ST-T wave abnormalities. An attempt was also made to identify different ZI biochemically through selective coronary sinus lactate sampling.

Comparison of these three separate lines of information was possible in 29 patients. A negative ECG (rest and postexercise) was seen in five patients, some of whom had extensive coronary artery disease; significant lactate production was seen in four of the five. In those 24 patients with identifiable ECG ZI, a coronary artery lesion corresponding to the site of this abnormality was noted in all, although multiple arterial lesions were associated with multiple ECG ZI in only six patients. Multiple ECG ZI, however, invariably indicated multiple vessel disease. Six of 29 patients had normal lactate metabolism, despite significant coronary lesions. Twenty-three patients had lactate ZI correlating with ECG ZI (site of venous lactate sampling versus ischemic ECG zone); 9 of 11 had single and 10 of 12 had

multiple ECG abnormalities. Single or multiple coronary lesions correlated with anticipated single or multiple lactate ZI in 24 of 29.

Thus, while the normal ECG is of no predictive value in coronary artery disease, the abnormal ECG accurately indicates a portion, but not necessarily the total, of the afflicted ZI. A high order of interrelation existed among sites of vessel lesion, sites of lactate production, and sites of ECG abnormality when either of the latter abnormalities was present in an individual case.

Prophylactic Digitalization

Antonio Hernandez, Jr., and David Goldring, St. Louis, Missouri

The prophylactic value of digoxin in preserving the height of contraction of atrial muscle strips which were subjected to anoxic stress was studied. After equilibration for one hour in an aerobic environment (95% $O_2 + 5\%$ CO_2), the strips were subjected to anoxic stress (95% $N_2 + 5\%$ CO_2) for one hour; and then allowed to recover again in an aerobic environment for one hour. The muscle strips were continuously stimulated. The contraction height at the end of the recovery period was compared with the height at the end of the equilibration period and expressed as percentage of recovery.

Atrial muscle strips from three groups of guinea pigs were studied. Group I was composed of 12 strips obtained from undigitalized guinea pigs; group II consisted of 11 strips from digitalized animals; and group III consisted of 10 strips from undigitalized animals; in group III, digoxin was added directly into the stimulating chamber during the equilibration period. The results showed that the mean percentage recovery of contraction height was 56% for group I, 75% for group II, and 90% for group III.

Twenty-two atrial muscle strips from patients undergoing open-heart surgery were made available for a similar study. Nine strips were obtained from undigitalized patients and 13 from patients digitalized preoperatively. The mean percentage recovery was 37.4% for the strips from undigitalized patients and 56.9% for the strips from patients who were digitalized preoperatively.

This study shows that digoxin aids in preserving the height of atrial muscle contraction after anoxic stress and suggests that patients undergoing open-heart surgery, whose hearts would be subjected to varying periods of anoxia, might benefit from prophylactic digitalization.

Tritiated Digoxin Study in Infants and Children

Antonio Hernandez, Jr., and David Goldring, St. Louis, Missouri

The purpose of this work was to study the absorption and excretion of digoxin in 18 patients with congenital heart defects who ranged in age from one week to two years; 16 were under six months of age. There were ten males and eight females. Thirteen had cyanotic heart disease and 15 manifested signs and symptoms of congestive heart failure. All were digitalized with tritiated digoxin (0.033 mg/kg body weight) and were maintained on 20% of their digitalizing dose. Eleven patients received the digoxin parenterally and seven orally. The period of study was 14 days; however, only eight patients completed the study period. Eleven patients expired because of their heart disease. Urine was collected daily and the radioactivity determined by scintillation technique. Chromatographic analyses of the urine samples were done by thin-layer chromatography. Samples of the heart, liver, and kidney of the patients who expired were also analyzed for radioactivity.

The results showed that the average daily excretion rate of digoxin in the group of patients who received the digoxin parenterally was 22% of the daily intake and 17% for the group that received the drug orally. The average urine concentration was 0.03 μg/ml for the group that received the drug parenterally, and 0.04 μg/ml for the oral group. Chromatographic analysis indicated that the radioactivity was due to unaltered digoxin. The average tissue concentrations of digoxin (μg/g of wet tissue) were: 0.21 in the kidney, 0.20 in the heart, and 0.09 in the liver.

Long-Term Benefits of Mitral Annuloplasty Versus Ball-Valve Replacement for Mitral Regurgitation (P)

Eugene A. Hessel, II, J. Ward Kennedy, and K. Alvin Merendino, Seattle, Washington

From 1956 to 1964, 57 patients with mitral regurgitation have had posteromedial annuloplasty. Of five with ruptured chordae tendineae, four remain in class I functional capacity, followed more than two years. Of nine with mitral regurgitation of rheumatic etiology, followed for five years, six had good or excellent results, while three have deteriorated. Of ten others with combined mitral regurgitation and stenosis who survived over four years, only two were improved and eight deteriorated, with one death. In 37 patients followed for three years postoperatively, 11 peripheral arterial embolic episodes (one renal, ten brain) have occurred in six patients, one had sequelae, and none died. In the past four years, operative deaths occurred in two of 28 patients (7%), and bacterial endocarditis has not been encountered. Operative mortality and the late postoperative complications from infection and embolism have been strikingly less than recently reported for replacement with Starr-Edwards ball-

valve prostheses in either local or cumulative national experience.

Divided Ureteral Urine Pressor Test in Renovascular Hypertension and Unilateral Parenchymal Renal Disease (P)

Roger B. Hickler, David P. Lauler, Adil E. Birbari, and J. Hartwell Harrison, Boston, Massachusetts

A comparison of the osmolar concentration of urine collected from each ureter is an established guide in screening hypertensive patients suspected of having unilateral renal disease. In only one patient out of 47 with essential hypertension was the variation of osmolar concentration between the two sides greater than 20%. Of 14 hypertensive patients with unilateral renovascular disease, 12 had urinary osmolar concentrations on the involved side 25 to 800% greater than those from the opposite side. In contrast, in ten hypertensive patients with unilateral parenchymal renal disease, osmolar concentration of urine from the involved kidney was decreased in every instance, ranging from 8 to 75% below that from the opposite side.

As a new, adjunctive test, fresh, iced urine was collected separately from each ureter and injected intravenously, in doses of 0.05 to 0.2 ml, into a pentolinium-blocked, vagotomized rat, and the ensuing rise in arterial pressure recorded. Of 46 patients with essential hypertension so tested, in only one instance was the difference in the rise in arterial pressure between the two sides greater than 50%. In all eight patients with renovascular hypertension similarly tested, there was a greater pressor response observed with urine from the involved kidney, ranging from 60 to 200% above that from the opposite side. In contrast, eight patients with hypertension associated with unilateral parenchymal renal disease all showed a decrease in pressor response with urine from the involved kidney, ranging from 30 to 80% below that of urine from the opposite side.

Open Intracardiac Repair for Complete Transposition of the Great Arteries (P)

Billy M. Hightower, William H. Weidman, and John W. Kirklin, Rochester, Minnesota

Between January 1, 1960, and April 1, 1965, 44 patients with complete transposition of the great arteries have undergone intracardiac repair resulting in a compensatory transposition of venous return. Patients' ages ranged from two months to 20 years. A total of 17 patients survived the operation and were dismissed home. There have been three late deaths. The greatest mortality has been in the 17 patients under one year of age (88%). Fifty-six per cent of the 27 patients over one year of age have survived. Long-term results have been excellent in surviving patients of all ages except for one case.

Associated defects other than atrial septal defect in surviving patients include ventricular septal defect (12 cases) and pulmonary stenosis plus ventricular septal defect (3 cases). One patient had previously undergone a Blalock-Hanlon operation. The ventricular septal defects and pulmonary stenoses were repaired at the time of the intracardiac operation.

During the past year, the Mustard-type operation has been utilized in 13 patients, with an overall survival rate of 69%. Preoperative hemodynamic data indicate that a pulmonary–systemic resistance ratio less than one is essential for the survival of the patient undergoing complete repair.

Gas Composition and Hemodynamic Changes in Using Respirators in Severely Ill Cardiac Patients

J. Donald Hill, F. Beachley Main, John J. Osborn, Robert W. Popper, and Frank L. Gerbode, San Francisco, California

Research and experience in the last five years have definitely established the value of controlled artificial respiration for the cardiac patient both preoperatively and postoperatively. There is, however, very little information available on the more advantageous methods of using respirators in varying types of cardiopulmonary insufficiency.

A group of patients who underwent open-heart surgery have been investigated upon their return to the recovery room. The Engström respirator has been used with varying degrees of end-expiratory pressure, volumes, gas composition, and rate to determine their effect on the cardiac output, left atrial pressure, aortic pressure, central venous pressure, arterial gas composition, and pulmonary compliance. These data have provided valuable information on how best to manage, with a respirator, common postoperative complications such as left- and right-heart failure, pulmonary edema, and hypoventilation. Of particular importance is the use of elevated end-expiratory pressures to elevate the arterial pO_2 above normal levels. This has been very effective in overcoming persistent pulmonary diffusion problems and has not shown any decrease in the cardiac output.

Hemodynamics, Clinical Features, and Course of Atrial Shunts in Infancy (P)

Julien I. E. Hoffman,† Delores Danilowicz, and Abraham M. Rudolph, New York, New York

Sixteen infants catheterized when four days to two months old had left-to-right atrial shunts as the sole or major cardiac abnormality. Two also

had tiny ventricular septal defects, one had a functionless patent ductus arteriosus, and four had systolic gradients of 6 to 18 mm Hg between main and peripheral pulmonary arteries.

Only one had cardiac symptoms and only one had subnormal weight gain. None had enlarged or hyperactive hearts. Only one had a wide, fixed split of the second heart sound. All had grade 2 to 3/6 systolic murmurs, maximal along the left sternal border and leading to the clinical diagnoses of patent ductus arteriosus, ventricular septal defect, or pulmonic stenosis. All X-rays were normal, and electrocardiograms were normal in all but three, who showed abnormal qR or R complexes in V_1.

At catheterization, pulmonic-to-systemic flow ratios were 1.2 to 4.6:1; all other hemodynamic findings were essentially normal. Left atrial mean pressure equaled right atrial mean pressure in one and exceeded it by 1 to 5 mm Hg in the others.

One child died from noncardiac causes, and the others have no cardiac symptoms. Four of six recatheterized patients have no shunts, and four others have lost their murmurs.

These studies indicate that left-to-right atrial shunts (often large) occur in infancy, are often asymptomatic, and need not be associated with cardiomegaly or wide, fixed splitting of the second heart sound. They can also disappear spontaneously. It is not known if the shunt occurs through a secundum atrial septal defect or an incompetent foramen ovale.

Influence of Intestinal Bacteria on 5α-Cholestan-3β-ol Metabolism

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Studies on the hypocholesterolemic effect of neomycin have shown that this antibiotic alters bile acid metabolism. We have therefore studied the influence of neomycin on the metabolism of 5α-cholestan-3β-ol (cholestanol), the saturated analogue of cholesterol. Cholestanol-fed rabbits develop gallstones (100% incidence) composed of the calcium and sodium salts of the glycine conjugate of allodeoxycholic (5α) acid. Allodeoxycholic acid is a secondary bile acid formed by bacterial dehydroxylation of the primary bile acid, allocholic acid. It was postulated that if such bacterial dehydroxylation could be prevented, allocholic acid would be present in bile, and gallstone formation might be prevented.

When rabbits were fed 0.5% neomycin and 1% cholestanol for four weeks, the population of aerobic coliform organisms in the feces decreased greatly. Bile analyses showed some increase in glycoallocholic acid and a marked decrease in glycoallodeoxycholic acid concentration, in addition to the glycodeoxycholic acid present normally. The neomycin thus appeared to decrease the rate of bacterial dehydroxylation of allocholic acid, and gallstone formation was prevented (12 animals out of 12).

These observations, plus in vitro experiments on the solubility of Ca^{++} salts of 5α- and 5β–bile acids, suggest that the precipitation of insoluble calcium salts in the gall bladders of cholestanol-fed rabbits is influenced by the dihydroxy/trihydroxy bile acid ratio, and that this ratio can be altered by appropriate antibiotics such as neomycin.

Efficacy of Gamma Globulin in the Prevention of Hepatitis After Open-Heart Operations

Paul Holland, Richard M. Rubinson, Paul J. Schmidt, and Andrew G. Morrow, Bethesda, Maryland

Post-transfusion hepatitis is responsible for significant morbidity, and occasionally death, in patients subjected to corrective cardiac operations performed with cardiopulmonary bypass. At our clinical center, the incidence of icteric hepatitis was 12% (24/200) in patients operated upon during 1962 and 1963. A prospective study was initiated, therefore, to determine whether the incidence of serum hepatitis in this patient population could be reduced by the prophylactic administration of gamma globulin, an agent of proven effectiveness in the prevention of *infectious* hepatitis.

Patients undergoing open-heart operations were assigned, on a random basis, to control and gamma globulin groups. Those given gamma globulin received 10 ml intramuscularly after the induction of anesthesia, and another 10 ml 30 days after operation. Patients in both groups were exposed to an average of 22 units of blood during and following operation.

Thirteen patients who survived six months or more developed icteric hepatitis. Of 77 patients given gamma globulin, nine contracted hepatitis, while four of 77 in the control group developed the disease. None of 27 children (< 12 years of age) developed hepatitis. Among older patients, the incidence was 6% (3/50) in those with congenital malformations, and 17% (10/77) in patients with acquired valvular disease.

The study indicates that gamma globulin, in the dose and schedule employed, is ineffective in preventing hepatitis following open-heart operations, and also that the risk of infection is distinctly higher in older patients with acquired heart disease.

Comparison of the Plasma Catecholamine Levels and the Influence of Propranolol on Peripheral Hemodynamic Manifestations of Emotional Stress in Labile Hypertensive and Normal Subjects (P)

Gunnar Holmberg, Lennart Levi, Alexander Mathé, Anders Rosén, Stockholm, Sweden, and Hugh M. Scott, Montreal, Quebec, Canada

More precise identification of the mode of production of the forearm vascular response to emotional stress in labile hypertensive patients compared with normal subjects has been attempted. Studies on such individuals were performed at rest and during two six-minute, rapid-mental-arithmetic (MA) periods one hour apart. Beta-adrenergic receptor blockade, tested with isoproterenol, was induced between the periods with 5 mg propranolol intravenously.

Forearm vascular resistance (intra-arterial mean pressure divided by water-plethysmographically measured forearm blood flow per minute) was similar in both groups at rest and in its sustained decrease during MA (eight hypertensive patients [mean $\pm$ SE], 6.0 ± 0.8 to 2.9 ± 0.5; seven normal subjects, 6.2 ± 0.6 to 2.7 ± 0.4). After propranolol, forearm vascular resistance did not decrease to the same degree during the second MA period (hypertensive patients, 6.5 ± 1.2 to 5.0 ± 1.2; normal subjects, 6.0 ± 0.6 to 4.7 ± 0.6). Mean systolic and diastolic pressures increased to the same degree during both MA periods, heart rate less during the second period.

Fluorimetric catecholamine analysis of successive arterial plasma samples from each subject revealed no epinephrine in any normal-subject samples, but did in samples from two of seven hypertensive patients. The mean norepinephrine concentration of initial resting samples was markedly higher in the hypertensive group than in the normal (0.6 ± 0.13 μg/L and 0.3 ± 0.05 μg/L, respectively). Slight or no increase was seen with MA.

It was concluded that β-adrenergic receptor stimulation, not necessarily epinephrine-mediated, is a prominent (but not the sole) mechanism producing forearm vasodilatation during emotional stress. Differences in the resting levels of plasma norepinephrine, heart rate, and systemic blood pressure, rather than in the patterns of response to emotional stress, were the significant features separating the two groups studied.

Coronary Arteriovenous Fistula and Aortic Sinus Aneurysm Rupture

John C. Holmes, Noble O. Fowler, and James A. Helmsworth, Cincinnati, Ohio

In local experience, coronary arteriovenous fistula or aortic sinus of Valsalva aneurysm rupture into the right heart are the two common causes of continuous murmurs with systolic accentuation which are maximum over the lower sternum. This report describes three patients with coronary arteriovenous fistula subjected to successful surgical repair, and five patients with anatomically verified aortic sinus aneurysm rupture, two of whom had successful repair.

Coronary arteriovenous fistula. Two patients were 20-year-old women; the third was a 24-year-old man. Two had increased arterial pulse pressure and heart failure, and each had cardiac enlargement. The dilated right coronary artery was demonstrated by aortography to communicate with the right ventricle in each instance. Surgical correction was followed by disappearance of the murmur and decrease in heart size.

Aortic sinus aneurysm rupture into the right heart. Each of the five patients demonstrated increased arterial pulse pressure and cardiac enlargement. Three had sudden onset of dyspnea; three had congestive heart failure; and one developed complete atrioventricular (A-V) block. Right-heart catheterization demonstrated entry of oxygenated blood into the right atrium or ventricle. Successful repair was carried out in two females, 14 and 22 years of age. In three men, aged 40 to 66 years, the communication caused eventual demise because of congestive heart failure, pulmonary hypertension, or complete A-V block.

Family Study of Coronary Heart Disease: Blood Pressure and Cholesterol Levels

Merton S. Honeyman, Henry Eisenberg, and John T. Morrison, Hartford, Connecticut

The Connecticut State Department of Health is engaged in an investigation of a number of variables in the offspring of myocardial infarction (MI) index cases hospitalized between 1940 and 1949, in order to determine if there is a greater frequency of myocardial infarctions among the offspring of MI index cases than among a control population. The control population consists of the spouses and siblings of the spouses of the MI offspring. This is a preliminary report of the observations of the blood pressure and cholesterol levels in 97 families of the MI index cases and 21 control families.

Comparisons of systolic and diastolic blood pressure levels and serum cholesterol level between the 243 offspring in the MI families and 88 individuals in the control families showed no differences. There were 64 MI families which had more than one offspring. These families showed significantly less variability within than between families for blood pressures and cholesterol levels. Analysis of the 21 control families revealed no

differences in the variability between and within families for these variables. This suggests that there is some familial factor present in the MI families which controls the variability of these families for these characteristics.

Examination of the correlation between 196 husband-and-wife pairs revealed no correlation for these variables, suggesting that the familial characteristic associated with the smaller within-family variation is not environmental.

Influence of Nutrition and "Acculturation" on the Blood Pressure Levels and Changes with Age in the Highland Guatemalan Indian (P)

Sibley W. Hoobler, Ann Arbor, Michigan, Carlos Tejada, Miguel Guzman, and Antonio Pardo, Guatemala City, Central America

Five hundred and ninety-eight adult, male, rural Guatemalan Indians, consisting of the majority of the inhabitants of the population sampled, exhibited a low mean blood pressure (113.4/72.6 at age 45) and little tendency for the level to rise between the ages of 20 and 60 years.

Two smaller subsamples, consisting of Indians of the same tribal origin but engaged in factory or managerial work in the midst of a westernized culture (Quetzaltenango), showed higher blood pressures, approaching the level of a small sample of Latin origin living in low socioeconomic circumstances.

Abdominal adiposity and increasing arm circumference correlated with the higher blood pressure, but could not entirely explain the highly significant differences among the populations studied.

It is concluded that subtle changes, occurring when primitive, primarily agricultural social groups become "accultured," are responsible for emphasizing or "expressing" the inborn and widely varying racial predisposition to develop elevated blood pressure with advancing age.

Determination of a Possible Sequence of Ventricular Activation in the Intact Dog (P)

Leo G. Horan and Nancy C. Flowers, Memphis, Tennessee

An equivalent electromotive ventricular surface of 233 dipolar facets was calculated for the dog and a table of transfer values consisting of the theoretical contribution of each facet to the electrocardiographic potential at 45 thoracic points was computed and placed in computer memory and combined with the transfer values. An initial guess as to the order of activation of the equivalent surface produced a theoretical set of surface potentials to be compared with those obtained experimentally. For each thoracic point, there now were two QRS waveforms—the actual and a theoretical analogue. Absolute correlation between the two sets was calculated. For each facet, 57 alternative orders of firing were examined as to effect on the analogue. Whenever a firing order improved the correlation between actual and analogous waveforms, the computer was instructed to adopt the new order of activation for that facet. After one survey of the 233 facets, the new sequence of activation of the equivalent ventricular surface raised the correlation coefficient from 0.17 to 0.55, and after ten such iterations, it exceeded 0.75, with slow improvement thereafter.

Representation of ventricular activation by an equivalent electromotive surface simulates anatomical and physiological characteristics of the real cardiac generator, but remains general enough to facilitate mathematical and physical manipulation. It may offer a convenient bridge (1) between electrocardiographic signals on the body surface and the actual dynamic spread of activation, and (2) between the more compact mathematical descriptions of the heart's activity (as the multipolar series or the principal factor group) and a physiologically or clinically meaningful portrait.

Cardiac Dysfunction Following Prosthetic Replacement of the Mitral Valve (P)

Harold J. Hubis and Herbert N. Hultgren, Palo Alto, California

Studies of cardiac performance from three to ten months after mitral valve replacement (Starr-Edwards prosthesis) have been carried out in 15 patients to determine the incidence and nature of suspected residual cardiac dysfunction. Cardiac catheterization studies were performed at rest and during supine exercise, and the effect of an infusion of isoproterenol (2 to 3 μg/min) was examined.

Although resting pulmonary arterial wedge pressure was normal in all patients, the following residual abnormalities were noted: (1) a reduced cardiac index at rest (mean, 2.5 L/min/m^2) and an increased arteriovenous oxygen difference (mean, 5.6 ml/100 ml); (2) an impaired cardiac output response to a standard exercise test (the mean increase in cardiac index was 27%, compared with a predicted value of 41%); and (3) an elevation of pulmonary arterial and pulmonary arterial wedge pressure during exercise (mean exercise values of 40 mm Hg and 20 mm Hg, respectively). Isoproterenol infusion produced a mean increase of 61% in cardiac output without elevation of pulmonary arterial wedge pressure. These abnormalities were not observed in similar studies carried out in seven patients with pros-

thetic replacement of the aortic valve. Neither obstruction to flow at the mitral orifice nor atrial fibrillation appeared to limit cardiac performance.

The data indicate impaired function of the left ventricle following replacement of the mitral valve with a prosthesis. Myocardial insufficiency as the result of chronic rheumatic heart disease or absence of normal papillary muscle function is probably an important responsible factor.

A Universal Discoid Valvular Prosthesis

Charles A. Hufnagel, Peter W. Conrad, and John F. Gillespie, Washington, District of Columbia

As ball and leaflet-type valves have demonstrated serious disadvantages, other forms of valve replacement have been investigated. A discoid valve has been developed for use in the mitral, aortic, tricuspid, and pulmonic positions and has been employed clinically since 1963. It offers several major advantages over previous methods of valve replacement. These include: (1) extremely light weight; (2) short travel of the occluding part; (3) minimal thrombus formation; (4) little protrusion into the ventricle or aortic root; (5) low impact of opening and closure; (6) minimal trauma to blood elements. An analysis of the clinical application of this type of prosthesis in all valvular positions has been made, together with the indications for use. The hemodynamics of this valve in relation to anatomical structure and the advantages of these relationships have been observed.

Vectorcardiographic Assessment of Left Ventricular Hypertension: Its Clinical Application to Aortic Stenosis and Coarctation of the Aorta

Paul G. Hugenholtz, Raul Gamboa, Laurence E. Wolf, and Alexander S. Nadas, Boston, Massachusetts

Hemodynamic and electrocardiographic studies were carried out in 31 patients with left ventricular hypertension due to aortic stenosis, and in 29 patients with left ventricular hypertension due to coarctation of the aorta, in an effort to confirm and extend a linear correlation between the spatial vectorcardiogram and left ventricular peak systolic pressure.

A new criterion, consisting of a sum of three spatial magnitudes (SMSV-3), yielded a better correlation ($r = 0.90$) than the previously advocated SMSV-4 ($r = 0.87$). Inclusion of patients with coarctation maintained the linear relationship ($r = 0.88$; SEE, 16 mm Hg). This easily obtained electrocardiographic parameter, when recorded with the corrected lead system of Frank, may prove to be the best criterion for recognizing left ventricular hypertension in a variety of lesions.

Less satisfactory correlation with the aortic valve area (AVA) was observed ($r = -0.45$). In 13 patients whose cardiac output and peripheral resistance were normal, the SMSV-3 related linearly to AVA ($r = -0.85$). Scrutiny of cases diverging from the regression line showed that chronic decreases in aortic valvular flow or peripheral pressure, leading to lowered peak pressure demands, were correctly reflected in SMSV-3, whereas acute changes in flow did not alter SMSV-3. These observations are in keeping with the concept that SMSV-3, of all factors determining cardiac work, relates chiefly to the average demand for peak systolic pressure, regardless of interindividual variations.

It is concluded that this type of analysis of spatial electromotive forces affords a simple and useful tool to the clinician in the assessment of left ventricular hypertension in patients with aortic stenosis or coarctation of the aorta.

Mitral Valve Prolapse: Clinical and Cineangiographic Observations

J. O'Neal Humphries, J. Michael Criley, and Kenneth B. Lewis, Baltimore, Maryland

A special form of mitral valvular dysfunction with a characteristic cineangiocardiographic appearance and a benign clinical course has been encountered in eight patients studied because of the clinical observation of a late systolic murmur. A systolic click introduced the murmur in four of these patients. Left-heart cineangiocardiography demonstrated aneurysmal bulging of one or both leaflets of the mitral valve into the left atrium in early systole, followed by mitral regurgitation in the latter part of systole in all eight patients. The systolic click, when present, correlated temporally with the maximal extent of prolapse of the leaflets. The late onset of the systolic murmur was correlated with the delayed appearance of valvular regurgitation.

Four patients had no significant medical histories, and the presumed etiologies in four other cases were Marfan's syndrome, gonococcal septicemia, periarteritis nodosa, and trauma. There was no evidence of coronary artery disease in any of these patients. Seven of them had no significant signs or symptoms.

These studies establish that some systolic clicks are of mitral valvular origin, and that murmurs confined to late systole may be indicative of a specific form of mitral regurgitation. The eight patients studied were selected from among 80 with similar clinical findings seen in the phonocardiographic laboratory during the past ten years.

Stimulation of Renin Secretion by Hydralazine: II. Studies in Renovascular Hypertension (P)

Andrew Huvos, Shigeru Yagi, John A. Mannick, and William Hollander, Boston, Massachusetts

The effect of hydralazine on renin secretion was studied in patients with hypertension associated with unilateral renal stenosis as demonstrated by aortography and by surgical exploration. Blood samples were obtained preoperatively by venous catheterization from both renal veins and from a peripheral vein. The patients were on an unrestricted salt diet and received no antihypertensive drugs for at least one month prior to the study. Renin activity was measured by rat bioassay. Of 13 patients with renal vascular hypertension, eight had increases in plasma renin activity, whereas five had normal renin levels. In those patients who had normal renin activity, intravenous hydralazine (20 mg) caused a marked increase of renin secretion from the involved kidney, but did not alter renin secretion from the uninvolved kidney. The increase in renin activity following intravenous hydralazine occurred even when the blood pressure did not fall following the administration of the drug. The effect of hydralazine on renin secretion was not counteracted by the β-adrenergic blocking agent, propranolol. Intravenous pentolinium produced a decrease in the blood pressure that was equal to or greater than that of hydralazine, but did not increase renin secretion. It is concluded that intravenous hydralazine stimulates renin secretion in hypertensive patients with renal arterial stenosis, including those who have normal pretreatment renin levels.

Late Manifestations of the Rubella Syndrome in the Adult

William H. Jacobs and Robert J. Marshall, Morgantown, West Virginia

The resurgence of interest in the rubella syndrome is explained by advances in two areas. First, hitherto unrecognized lesions, such as multiple peripheral stenosis of the pulmonary arteries and the neonatal syndrome of purpura, thrombocytopenia, hepatosplenomegaly, encephalomyelitis, and bone lesions, have been clearly described. Second, it has been shown that the virus is transferred transplacentally to the developing fetus, and that it may continue to be excreted by the newborn infant and infect adult contacts. Late manifestations of the rubella syndrome have escaped attention in adults, probably because the patent ductus arteriosus has usually been diagnosed and treated surgically in earlier life, and because a history of a transient maternal exanthem has long since been forgotten.

We have studied two women, aged 35 and 23 years, with classical features of the rubella syndrome. These included severe growth retardation (body weights were 68 and 91 pounds), congenital cataracts, congenital deafness, multiple skeletal defects, bicornuate uterus (one case), and a well-documented history of maternal rubella (one case). Each had a patent ductus arteriosus, severe pulmonary hypertension, and reversal of the shunt, with differential cyanosis of the lower extremities. Serial studies in the first patient demonstrated rapidly progressive obliterative changes in lung vessels, in that the pulmonary vascular resistance increased from 32 to 53 units. These cases are reported because they illustrate the opposite end of the spectrum from that involving the fetus and neonate, which is currently the focus of attention.

Ultrastructure of the Human Sinus Node (P)

Thomas N. James, Libi Sherf, Gerald Fine, and Azorides R. Morales, Detroit, Michigan

Ultrastructure of myocardium has been frequently studied, but the conduction system has heretofore been described only in subhuman species. The findings that postmortem changes in myocardium are relatively few within the first hours after death have been confirmed. Employing familiarity with the anatomy of the sinus node and atrium derived from study of 208 human hearts, we have examined the ultrastructure of the sinus node and right atrium of two human hearts fixed three hours after death, compared the atrium with an in vivo human biopsy, and compared both with node and atrium obtained in vivo from the dog.

The characteristic cell of the human sinus node is round or oval. Its smooth double-layered membrane contrasts with the scalloped membrane of atrial cells. Myofibrils within the sinus cells are sparse in number, contain few filaments, and course in all directions. Intercellular contacts are frequent in all directions, with the plasma membranes becoming apposite while the basement membrane bridges over adjacent cells. Scattered desmosome-like structures occur at these contacts, but organize into intercalated discs only in intermediate cells. Intermediate cells gradually increase in content of myofibrils, which contain more filaments, and these cells elongate until they resemble ordinary myocardium. Sarcosomes are distributed randomly in sinus cells, but are packed between myofibrils in atrial myocardium. Intercellular clefts in the sinus node contain fibrocytes, nerves, and collagen. The ultrastructure of the human sinus node closely resembles that of the dog.

Low-Molecular-Weight Dextran, Blood Flow, and Peripheral Resistance

Gregory N. Jelinek, Richard M. Wolfman, and Jackson H. Stuckey, Brooklyn, New York

Previous studies have not correlated blood flow, peripheral resistance, plasma volume, and viscosity findings with known low-molecular-weight dextran (LMD) concentrations in blood plasma. The purpose of this report is to present our initial observations in a continuing study designed to explore any existing correlations.

Each of five anesthetized, healthy, mongrel dogs was rapidly infused with 1 g/kg LMD (40,000; 15% dextran in 5% dextrose). Arterial pressure, blood flow, electrocardiogram, plasma volume, dextran concentration in plasma, and viscosity were recorded.

Arterial blood pressure showed little variation throughout the experiment. Blood flow increased 70% following LMD infusion, and remained above pre-LMD levels for 60 minutes and above control levels for 150 minutes. Plasma volume increased three times the volume of dextran infused and remained above control levels for 90 minutes. Peripheral resistance decreased below predextran levels for 60 minutes. Dextran concentrations initially decreased rapidly, reaching 0.5 g/100 cc within 75 minutes. This rapid decrease was followed by a slower constant decline, with plasma LMD concentrations reaching 0.37 to 0.39 g/100 cc blood at four hours postinjection. Whole-blood viscosity decreased with high plasma dextran concentrations (0.8 g/100 cc), while plasma viscosity increased; with lower plasma dextran concentration (0.4 g/100 cc), viscosity values were closer to predextran levels. It may be concluded, therefore, that:

1. High concentrations of LMD resulted in an increase of blood flow and plasma volume and in a decrease of peripheral resistance.
2. LMD increases plasma viscosity, decreases viscosity of the red cell component, and decreases whole-blood viscosity.
3. LMD increases blood flow beyond the plasma expansion effect.

Chemical Determinations of Urinary Digitoxin and Digoxin Excretion and Metabolism (P)

Roger W. Jelliffe, Los Angeles, California

Clinical studies of urinary digitoxin and digoxin excretion have been performed, using a chemical determination of these urinary glycosides developed in this laboratory. Urinary excretion values and glycoside turnover rates have been determined, and the metabolic hydroxylation of digitoxin to digoxin in man has been quantified for the first time.

Twenty undigitalized patients excreted up to 11.5 μg/day of substances resembling digitoxin (mean = 3.18 μg, SD = ± 3.27 μg) and up to 12.5 μg/day of substances resembling digoxin (mean = 1.41 μg, SD = ± 6.49 μg).

In contrast, five patients receiving 0.25 to 1.0 mg oral digoxin/day excreted 74 to 220 μg digoxin/day, approximately 25% of the dose. No digitoxin was found. Eight patients receiving 0.1 to 0.3 mg oral digitoxin/day excreted 11 to 44 μg digitoxin/day, approximately 15% of the dose. Some patients also excreted significant amounts of digoxin, while others did not.

Prolonged studies were performed on three patients. Two were digitalized and maintained with oral digoxin; 25% of the dose was excreted unchanged, with a urinary T½ of 20 and 33 hours, respectively. No digitoxin was excreted.

One patient was digitalized and maintained with oral digitoxin; 15% of the dose was excreted as unchanged digitoxin, with a urinary T½ of 3.5 days. Furthermore, 8% of the dose was excreted as digoxin, with maximum excretion (35 μg/day) occurring on the fifth day after digitalization. Assuming 60 to 80% absorption and 25% excretion of oral digoxin, and assuming 100% absorption of oral digitoxin, this patient converted 19 to 26% of the administered digitoxin to digoxin.

Lymphatics of Arteries

Robert A. Johnson and Thomas M. Blake, Jackson, Mississippi

This study was undertaken to delineate the anatomy of lymphatics in arterial walls. Aortas and coronary arteries of humans and pigs were studied by topical application of hydrogen peroxide, injection of India ink, clearing, stereomicroscopic dissection, and photography.

Fine networks of lymphatics are present in the adventitia of the aorta in both species, with drainage, via collecting channels, either directly into the thoracic duct or into regional nodes. No lymphatics have been identified in either the media or intima or atheromata. In pig aortas, lymphaticovenous anastomoses make it difficult to identify with certainty the smallest channels as either blood vessels or lymphatics.

In the adventitia of subepicardial coronary arteries and veins, the lymphatics form networks in continuity with the subepicardial plexuses, with small channels oriented longitudinally and transversely to the underlying vessel; but lymphatics have not been found deep to the adventitia.

Lymphatics have not been demonstrated in the media or intima of arteries or in atheromata, but are prominent in the adventitia of the large arteries studied.

Acute Hypoxia: Tachycardia or Bradycardia?

John R. Jones, Randhir S. Sandhu, and James R. Adwers, Omaha, Nebraska

An initial tachycardia is accepted as a sign of hypoxia. Studies in laboratory animals and man have shown this to occur when the subject is placed in an ambient atmosphere low in oxygen tension. A chance observation of bradycardia made in our laboratory led us to examine this thesis more closely.

Mongrel dogs were used after a quarantine period and suitable inoculations to exclude any illness which might affect the heart. They were anesthetized with pentobarbital and intubated with a cuffed endotracheal tube. Blood pressure, heart rate, and electrocardiograms were monitored and recorded continuously. Arterial pO_2, pH, and pCO_2 were obtained with blood gas electrodes. Nitrogen was added to the inhaled atmosphere to produce hypoxia.

Fourteen observations were made on dogs breathing spontaneously. Hypoxia produced tachycardia in 13 and no change in one; this confirmed the work of many others. Next, 14 observations were made with ventilation controlled by a piston respirator. Five had an increase in pulse rate, two had no change, and seven had a *decrease* in pulse rate. As these animals became hypoxic, attempts at spontaneous respiration became apparent. Twenty-one observations were then made with the animal on a ventilator but having received succinylcholine in addition. Seven had an increase in pulse rate, four had no change, and ten had a *decrease* in pulse rate.

In order to test the hypothesis that compensatory mechanisms are responsible for the tachycardia seen in hypoxia, 15 observations were made on perfused, isolated guinea pig hearts. As the oxygen tension was lowered, *all* had a decrease in rate.

Preoperative Determination of the Functional Anatomy of the Mitral Valve (P)

Claude R. Joyner, Jr., Ihor Dyrda, John S. Barrett, and John M. Reid, Philadelphia, Pennsylvania

The echo-ranging technique has been used to obtain ultrasound time-distance patterns of mitral valvular motion from 870 subjects. The normal curve has two peaks of anterior motion into the left ventricle. One peak follows the P wave of the electrocardiogram and is absent in atrial fibrillation. The most prominent peak of anterior motion is inscribed as the valve opens after the T wave. This early diastolic peak is followed by rapid posterior movement of the valve during ventricular filling. The velocity of the posterior motion was greater than 85 mm/sec in normal subjects and less than 40 mm/sec in 260 patients with mitral stenosis. Velocity measurements correlated well with orifice size and permitted accurate preoperative assessment of the degree of mitral stenosis, regardless of whether the valvular substance was thin or thickened.

The character of the substance of the mitral leaflet, determined at operation or necropsy, has been compared with the ultrasound pattern in 112 subjects. The normal echo from the anterior leaflet of the mitral valve is 1- to 3-mm wide, with a total anterior-posterior motion of 2.5 to 3.5 cm. Stenotic valves with thin and pliable leaflets showed a 2- to 4-mm wide echo, with normal or near-normal total excursion. Increasing thickness of the valve due to calcification or fibrous tissue caused an increase in the width of the echo and a decrease in anterior-posterior excursion. Very thick valves had echoes 10- to 12-mm wide, with total anterior-posterior motion of under 1 cm. Patients with no radiologically demonstrable calcification, but with thick, restricted echoes, were found at surgery to have thick fibrous valves with fused chordae. Three patients with dense calcification by fluoroscopy, but thin echoes with good excursion, were found to have annulus calcification with pliable leaflets.

Ventricular Response to Exercise and Isoproterenol in Atrioventricular Dissociation due to Congenital or Acquired Apparent Complete and Advanced Heart Block in Children (P)

Kenneth L. Jue, Minneapolis, Minnesota, Herbert D. Ruttenberg, Los Angeles, California, Ray C. Anderson, and Paul Adams, Jr., Minneapolis, Minnesota

Because of the paucity of hemodynamic data available in the literature concerning congenital and acquired atrioventricular (A-V) block in children during exercise, this study was undertaken to determine the ventricular response to exercise and isoproterenol in nine patients with congenital or acquired heart block, utilizing dye-dilution techniques to determine cardiac output.

The study demonstrated that the cardiac index (CI) was normal in all patients at rest. In five patients with A-V dissociation due to congenital apparent complete heart block, the stroke index (SI) was elevated at rest. During exercise, the CI was augmented by increases in both SI and ventricular rate (VR). Two patients with A-V dissociation due to surgically acquired advanced heart block responded to exercise in all respects similarly to the above group. In two patients with A-V dissociation due to surgically acquired apparent complete heart block, the response during

exercise differed in that no increase in CI was observed.

The response to isoproterenol infusion (0.8 μg/min) paralleled the response to exercise in all groups except the group with surgically acquired apparent complete heart block, in which the increased CI was related only to increased VR, rather than to both VR and SI.

This study showed that patients with A-V dissociation due to either congenital apparent complete heart block or surgically acquired advanced heart block responded similarly to exercise and isoproterenol, and that the latter group could be differentiated from patients with A-V dissociation due to surgically acquired apparent complete heart block by the response to exercise.

Artificial Pacemakers in the Treatment of Heart Block: Importance of Supplemental Drug Therapy (P)

George C. Kaiser, Vallee L. Willman, Theodore Cooper, and C. Rollins Hanlon, St. Louis, Missouri

In the treatment of heart block by insertion of an implantable pacemaker, some have assumed that successful modification of the bradycardia was essentially the only treatment required. Thirty of our 34 patients treated by pacemaker insertion had been receiving medication for congestive heart failure at the time of operation. Withdrawal from digitalis and diuretics in some of these patients has shown the need for sustained drug therapy even after the pacemaker implantation.

Quinidine or procainamide hydrochloride was employed in the treatment of six patients. In three, whose Stokes-Adams attacks were due to ventricular tachycardia and fibrillation, myocardial irritability was treated with these agents before and after operation. An additional patient required quinidine for coupling and a pulse deficit 14 months after implantation of the pacemaker.

Four patients required prolonged vasopressor therapy after operation, despite adequate pacing. In one of these patients, the hypotension was presumably due to a myocardial infarction; in the remaining three instances, there were serious ventricular arrhythmias. Metaraminol or norepinephrine was effective in two instances; in two others these drugs contributed to arrhythmias. One of the latter patients responded readily to phenylephrine hydrochloride.

Left atrial and left ventricular biopsies from seven patients at the time of operation demonstrated depletion of myocardial catecholamine stores. This suggests that loss of sympathetic support may contribute to the decompensation associated with heart block. It also provides one possible explanation of the need for supplemental drug therapy in operative treatment of heart block.

Relationship Between Endogenous Fuel and Performance of Isolated Hearts of Fed, Starved, and Alloxan Diabetic Rats

Kyohei Kako, Ottawa, Ontario, Canada

Bing showed that in hearts in situ, most of the energy of cardiac contraction is derived from oxidation of lipids. Long-chain fatty acids are readily taken up, oxidized, and even stored by the myocardium. In isolated perfused rat hearts, however, the oxygen extraction ratio of substrates taken up never reaches 100%, suggesting oxidation of stored fuel. Changes in myocardial contents of glycogen, triglyceride, phospholipid, cholesterol, free fatty acids, and high-energy phosphates, during perfusion of rat hearts with the Langendorff technique, were determined in this study. The perfusate was Zaccharia's bicarbonate buffer, with or without dialyzed bovine albumin. The experiments in which the coronary flow was less than 5 ml/min or effluent pO_2 less than 150 mm Hg were rejected.

Average qO_2 during one hour's perfusion was 33 ml/g of dry weight/hour for fed, starved (48 hours), and alloxan diabetic rats. Myocardial glycogen content of starved and diabetic rats was higher (20 to 25 mg/g dry weight) than that of fed rats (5 to 10 mg/g); its consumption during perfusion was more rapid by the hearts of the former (accounting 53% of qO_2; 14.6 of 27.5) than those of the latter (16.4% of qO_2; 4.5 of 27.5). The rate of breakdown of phospholipid and triglyceride during perfusion did not show a significant difference among the three groups, although the concentration of these two components always decreased. Cholesterol and free fatty acids showed no change. Phosphoryl creatine, lactate, and ATP tend to decrease during substrate-free perfusion.

A decrease in contractility appeared to occur parallel to a loss of tissue glycogen and phosphoryl creatine. Some of the intermediates of carbohydrates or of the Krebs cycle appeared to be essential for maintenance of cardiac performance, as well as for oxidation of lipids in isolated perfused rat hearts.

Epidemiological Aspects of Intermittent Claudication: The Framingham Study (P)

William B. Kannel, Thomas R. Dawber, John J. Skinner, Jr., Patricia M. McNamara, Framingham, Massachusetts, and Dewey Shurtleff, Bethesda, Maryland

A study population of 5,111 men and women aged 30 to 62 years, initially free of both coronary

heart disease and intermittent claudication, was classified according to: blood pressure status, serum cholesterol, electrocardiographic observations, cigarette-smoking habit, relative weight, blood and urine sugar, vital capacity, and combinations of these. By observation of the incidence of intermittent claudication in the population so classified, the magnitude of the risk associated with these factors was estimated. In 12 years, 38 men and 13 women developed unequivocal intermittent claudication. The marked male predominance became less pronounced with advancing age.

Individuals highly susceptible to intermittent claudication had one or more of the following: elevated serum cholesterol level, hypertensive vascular disease, ECG abnormalities, and the cigarette-smoking habit. Overweight could not be demonstrated to predispose to claudication. In women over 50 years, "elevated" serum cholesterol level was not associated with excess risk. Subjects with combinations of these factors ran an extremely high excess risk of intermittent claudication as well as coronary heart disease and brain infarctions. Persons developing intermittent claudication had more than a threefold excess risk of acquiring brain infarction or coronary heart disease. Diabetics developed a striking excess of intermittent claudication, as well as coronary heart disease and brain infarction.

In contrast with cases of coronary heart disease, the vast majority developing claudication were under medical care and ill, principally with cardiovascular disease. Since the epidemiological features of intermittent claudication and other atherosclerotic diseases were similar, measures taken to delay the onset of any one would, if successful, very likely be effective in preventing the others, including intermittent claudication.

Exercise Therapy for Angina Pectoris (P)

Albert A. Kattus and Rex N. MacAlpin, Los Angeles, California

Twenty-nine subjects with well-documented angina pectoris were placed on an unsupervised program of walking exercise which was increased gradually to the equivalent of one to four miles of extra walking daily. Initial evaluation included objective measurement of exercise capacity on a treadmill, with continuous electrocardiographic monitoring.

Satisfactory follow-up data have been obtained on 19 of these subjects 1 to 24 months (average, six months) after institution of exercise therapy. Subjective improvement in exercise capacity and lessening or disappearance of anginal symptoms were claimed by 13 of these 19 subjects, and improvement could be objectively documented in 11 of these by the presence of a 200% to 700% (average, 500%) increase in exercise capacity at repeat treadmill testing. Ten of these 11 subjects had demonstrated an ability to adapt to exercise on their initial treadmill tests by being able to walk right through an attack of angina pectoris or by having marked improvement in exercise capacity after being warmed up by a preceding bout of exercise-induced angina. Of seven subjects not showing this ability to adapt to exercise on initial testing, only one subsequently showed objective evidence of improvement after a period of exercise therapy.

It is believed that certain patients with angina pectoris will benefit by a regular program of walking exercise, and that those most likely to derive this benefit can be preselected by their response to careful initial treadmill testing.

Surgical Treatment of *Candida* Endocarditis

Jerome H. Kay, Sol Bernstein, Mildred Milgrom, Harold K. Tsuji, and Marjorie Biddle, Los Angeles, California

Five years ago, a patient was operated upon for a ventricular septal defect and *Candida albicans* endocarditis. The nidus of infection was removed from the tricuspid valve and the ventricular septal defect was closed. He is cured of the *Candida albicans* infection as well as the ventricular septal defect. With this patient's excellent result, we were encouraged to operate upon two patients with *Candida* endocarditis associated with pronounced aortic insufficiency. One patient with a *Candida albicans* endocarditis and another with *Candida krusei* were therefore operated upon. Both of these patients had pronounced aortic insufficiency. The organism was found to be growing on the valve in both of these patients, and there was almost complete destruction of the aortic valve in both patients. In one patient, there was also mitral insufficiency due to annular dilatation, as well as areas of destruction due to the *Candida albicans*. The mitral valve was repaired in this patient with stainless steel sutures, and in both patients the aortic valve was removed and replaced with a Magovern ball valve, without the Ivalon sponge insert. The patients were both treated with amphotericin B postoperatively. They are now 12 and 14 months after surgery; both appear to be doing well, without evidence of infection.

It would appear that a more aggressive approach toward the surgical treatment of *Candida* infections of the heart should be taken when they are associated with operable cardiac lesions. It is believed that these are the first patients operated upon successfully for *Candida* endocarditis.

Effect of Nicotinic Acid, Tobacco Substitutes, and Special Filters on the Free Fatty Acid Mobilizing Effect of Cigarette Smoking

Alfred Kershbaum, Samuel Bellet, and Jose Jimenez, Philadelphia, Pennsylvania

It has previously been shown that cigarette smoking causes a rapid and consistent mobilization of free fatty acids (FFA). In this study, various agents were used in an attempt to modify this effect. In one group of subjects, nicotinic acid (200 mg orally) was given 30 minutes before smoking two cigarettes (filter). There was a fall in FFA concentration after nicotinic acid, and the usual rise after smoking was abolished. On the basis of these results, nicotinic acid appears to have a sympatholytic effect on basal FFA levels, and an inhibitory effect on nicotine-induced FFA mobilization similar to that of an adrenergic β-receptor blocker.

In a second group of subjects, the FFA effect of smoking special cigarettes was observed. In all experiments, two cigarettes were smoked in ten minutes and FFA concentrations determined at intervals for 40 minutes. With cigarettes containing shredded lettuce leaves in place of tobacco, there was no change in serum FFA levels. After charcoal-filter cigarettes, there was an FFA rise similar to that occurring after regular filter cigarettes. Cigarettes containing pipe tobacco produced the same FFA response as standard cigarettes.

These results indicate that smoke from burned tobacco causes FFA mobilization, regardless of the cut of the leaf, and this does not occur with lettuce-leaf smoke.

Comparative Effects of Cigar and Cigarette Smoking on Free Fatty Acid Mobilization and Catecholamine Excretion

Alfred Kershbaum, Samuel Bellet, Jose Jimenez, and Leonard J. Feinberg, Philadelphia, Pennsylvania

Epidemiological studies have shown that the increased incidence of coronary heart disease associated with cigarette smoking does not occur with cigar smoking. An explanation for this may be found in differences in the biological effects of the two types of smoking. In this study, the relative effects of cigar and cigarette smoking on free fatty acid (FFA) mobilization and catecholamine activity were investigated.

Normal male subjects smoked one-half a cigar in a 20-minute period, consuming 3 g of tobacco containing approximately 2% nicotine; the customary method of cigar smoking (not inhaling) was used. There was a mean rise in serum FFA of $7 \pm 3\%$. In a matched group of subjects smoking three cigarettes (inhaling) with the same total tobacco and nicotine content, there was an FFA elevation of $36 \pm 4\%$ ($P < 0.001$). Six subjects smoking cigars and cigarettes on alternate days also showed a much smaller increase in FFA concentration after cigar smoking.

Experiments to determine the influence of inhaling on the difference in FFA response revealed the following: (1) cigar smokers developed higher FFA levels with inhaling than with not inhaling; (2) cigarette smokers had lower FFA concentrations when not inhaling than when inhaling. In other studies, cigars and cigarettes containing C^{14}-labeled glucose were smoked; less radioactivity was detected in the blood after cigar smoking.

Urinary catecholamine excretion was measured in 11 subjects by a fluorometric technique while they were smoking cigarettes, smoking cigars, and during a fasting control period. Total free catecholamine output during a four-hour period was 5.76, 3.97, and 2.59 μg norepinephrine equivalents, respectively; differences were statistically significant.

The results indicate that FFA mobilization and catecholamine excretion are less with cigar smoking than with cigarette smoking, probably because less nicotine is absorbed from the non-inhaled cigar smoke.

Carotid Sinus Baroreceptor Mechanism and Postganglionic Sympathetic Nerve Discharge (P)

Paul Kezdi and Eran Geller, Chicago, Illinois

To determine the relationship of the baroreceptor (carotid sinus) afferent input to postganglionic splanchnic and renal sympathetic nerve discharge, the isolated carotid sinus was perfused bilaterally by four different pressure forms: constant pressure of different levels; sinusoidal pressure of varying mean with constant amplitude and frequency; sinusoidal pressure of varying frequency with constant mean and amplitude; step pressure changes. The aortic depressor nerves were cut. Carotid and systemic pressures, respiration, renal and splanchnic postganglionic sympathetic and carotid sinus nerve impulses were recorded on tape. Computer counting and averaging techniques were used to determine the quantitative relationship between the carotid sinus baroreceptor input to the vasomotor center and the sympathetic discharge.

The experiments indicated that postganglionic (renal and splanchnic) sympathetic discharge is, to a large extent, controlled by baroreceptor and respiratory center inputs, acting on the vasomotor center. Computer averaging techniques allowed functional separation of the effects of these two inputs on sympathetic discharge. Response of the system to varying levels of mean and sine-wave pressures followed a reversed S-

shaped curve and was approximately linear within physiological pressure range. Sine-wave pressures elicited a proportionally larger response in comparison with steady pressures. The delay from carotid sinus input to postganglionic sympathetic discharge was around 300 msec. The sympathetic discharge followed the frequencies of the carotid sine-wave pressures approximately between three decades (0.01 to 10 cycles/sec). The gain of the system decreased and the phase shift increased with increasing frequency of stimulation.

Assessment of a Catheter-Tip Thermodilution Method for Cardiac Output Determination in Man in Comparison with the Direct Fick Method (P)

Hassan H. Khalil, Maylene Wong,‡ and Elliot Rapaport, San Francisco, California

We compared the cardiac outputs obtained by a new catheter-tip thermal dilution method using a heat generator with those obtained simultaneously by the direct Fick method in man.

The thermal dilution method consists of a single catheter which has an enameled constantan wire coil wound along the surface of the catheter nearer to its distal than to its proximal end and a resistance thermometer wound around its distal end. The catheter is placed in the normal manner into the pulmonary artery. Heat is generated from the coiled wire with a high-frequency alternating current for a given period of time, so that a known amount of heat energy is transferred into the blood at a constant and continuous rate. The resistance thermometer records the change in temperature in the pulmonary artery as a new plateau temperature is reached. The method is analogous to and based on the same principle as the continuous dye-infusion method, except that positive heat is used instead of dye. It has a major advantage over the dye method in that the body acts as a very large heat "sink," so that there is almost no recirculation.

The method was applied to 11 patients during routine cardiac catheterization. The ratio of the cardiac outputs obtained by this thermal dilution method to those obtained by the direct Fick method was 1.02 ($S = 4.4\%$). We conclude that this method offers a simple and accurate technique for repeated cardiac output determinations in man.

Hemodynamic Effects of a Totally Corrective Procedure in Complete Transposition of the Great Vessels (P)

Langford Kidd and William T. Mustard, Toronto, Ontario, Canada

Four patients who have undergone a new, totally corrective procedure for complete transposition of the great vessels have had cardiac catheterization before and after this operation. All had had an atrial septal defect created in early infancy, and were aged 17 to 28 months. They all had systemic desaturation before operation and had pressures less than systemic in the left ventricle. One patient had a very small ventricular septal defect; three had a closed ventricular septum. Postoperatively, the systemic oxygen saturation was 96, 94, 94, and 96%, respectively; the pressures in the new right atrium, passing systemic venous blood to the left ventricle and pulmonary artery, were 6, 4, 3, and 5 mm Hg. It was possible in two cases to pass a catheter behind the pericardial baffle to the new left atrium, delivering pulmonary venous blood to the right ventricle and aorta, and the pressures recorded were 4 and 2 mm Hg. One of these patients had a small shunt at the atrial level which was toward the pulmonary circulation, suggesting that ventricular compliance may be altered in transposition. The cardiac index was normal in the other three cases. Angiocardiography demonstrated the new atrial chambers to be adequate in size, and atrial pressure tracings suggested that they were functioning as atria and not as single blood-conducting passages. Exercise or other stress was not applied during catheterization, but full systemic saturation persists on exertion. All four children continue to do well postoperatively.

Salt and Water Paradox to Oxygen in Cor Pulmonale (P)

Kaye H. Kilburn and Anthony R. Dowell, Durham, North Carolina

Seventeen patients with respiratory failure (PaO_2 below 50 mm Hg or $PaCO_2$ above 60 mm Hg) due to obesity, emphysema, or pulmonary fibrosis had gross edema. The edema was refractory to rest, salt restriction, digitalis, and diuretics, but 20- to 65-pound weight losses occurred in five to ten days during continuous oxygen breathing. While the patients were in respiratory failure, only 11 to 25% of a 1,500-ml water load was excreted in four hours, compared with more than 50% after recovery. When CO_2 retention resulted from oxygenation, urinary flow decreased. Renal clearance studies showed increased urinary output and renal plasma flow (RPF) during O_2 tensions below 40 mm Hg. In contrast, five patients responded to oxygenation with reduced urinary flow and RPF. Glomerular filtration rates were reduced, but were unchanged by blood gas alterations. When arterial blood oxygen tensions were below 35 mm Hg, further reductions decreased urinary volume and RPF; however, reduction of O_2 down to this level increased RPF. Increased oxygenation, particularly above tensions

of 100 mm Hg, reduced urinary flow and RPF significantly.

Urinary volume, osmolar clearance, and sodium excretion were studied in six well-hydrated, thiopental-anesthetized dogs. Exposure to 10% O_2 increased urinary flow in some dogs and decreased it in others, compared with air breathing; but 40% O_2 had no effect. Breathing 10% CO_2 decreased urinary flow and greatly increased sodium excretion, an effect not previously reported.

Observations on patients with fluid retention during respiratory failure and acute studies of renal function demonstrated critical permissive ranges of arterial blood oxygen between 40 and 100 mm Hg and carbon dioxide below 60 mm Hg. Outside these ranges, renal plasma flow is reduced and urinary output, including the output of sodium, is altered.

Short- and Long-Term Results from Direct-Current Conversion for Atrial Fibrillation and Flutter

Thomas Killip and Stanley Yormak, New York, New York

One hundred and thirty-five consecutive patients with atrial flutter or fibrillation undergoing 174 attempted conversions with d-c shock have been followed for one year. Ventricular fibrillation occurred during thiopental anesthesia in one patient and following d-c shock in another. Sinus rhythm was induced in 152 attempts (87%). All patients but those with treated thyrotoxicosis were maintained on quinidine, 1.2 to 1.6 g, or procainamide, 2.0 to 4.0 g, daily. One-third of the patients could not tolerate drugs, and another third discontinued medication voluntarily. Sinus tachycardia and pulmonary edema followed reversion in two patients with mitral stenosis. Post-reversion systemic emboli occurred three times and pulmonary emboli twice. Unexpected cardiac arrest due to ventricular fibrillation was encountered in six patients within 48 hours of reversion, and three died. Two patients had episodes of unconsciousness during relapse from sinus rhythm.

The long-term percentage of 115 patients remaining in sinus rhythm after successful reversion from atrial fibrillation has been as follows: one hour, 94; one day, 84; one week, 72; one month, 60; six months, 39; one year, 27. Results for atrial flutter are similar. The duration of arrhythmia was not correlated with persistence of sinus rhythm. After one year, sinus rhythm was maintained in 6 of 13 (46%) patients with mitral regurgitation and 7 of 50 (14%) patients with mitral stenosis ($P < 0.02$). The duration of sinus rhythm in patients with rheumatic heart disease was not significantly different than in those with nonrheumatic causes.

Despite ease of application and high initial reversion rate, significant complications may occur with d-c shock. Long-term results are disappointing, and emphasize inadequacy of present techniques for maintenance of sinus rhythm.

Ascending Aorta—Main Pulmonary Artery Shunts in Cyanotic Heart Disease

Harold King and H. Gibbs Andrews, Indianapolis, Indiana

Although subclavian to pulmonary artery anastomosis (Blalock) continues to be a satisfactory operation for the preliminary operative treatment of severe tetralogy of Fallot, an adequate shunt cannot be created in all cases. Descending aorta to left pulmonary artery shunt (Potts) is now to be avoided because of the great difficulties associated with closure of the anastomosis at the time of intracardiac repair. Other described alternative procedures require the use of grafts or division of the pulmonary artery.

Since January of 1964, shunts have been created between the ascending aorta and main pulmonary artery by side-to-side anastomosis in two patients with severe tetralogy of Fallot and in one with pulmonary atresia. Their ages at the time of operation were six weeks, eight months, and seven years. Two had small distal pulmonary arteries and were not candidates for a subclavian–pulmonary artery shunt. In the third patient, subclavian to pulmonary artery anastomoses had previously been carried out, both on the right and the left, but cyanosis continued. All patients survived and were improved.

This procedure offers certain advantages. A shunt of adequate size can be accomplished in most patients, since the only limiting factor is the size of the main pulmonary artery. Arterial blood flow to the arm is not diminished. Shunt flow serves both lungs rather than predominately the ipsilateral side. The shunt can probably be closed relatively easily at the time of intracardiac repair.

Detection of Patients with Renal Hypertension and Results of Surgery (P)

Walter M. Kirkendall, Annette E. Fitz, Montague S. Lawrence, and David A. Culp, Iowa City, Iowa

From January, 1962, through February, 1965, surgical procedures for renal hypertension were done in 50 patients at the University of Iowa Hospitals. Eleven patients who were cured (C) had postoperative blood pressures (BP) below 140/90 without therapy; 15, considered improved

(I), had a fall in mean BP of at least 20 mm Hg postoperatively, without additional therapy. Nineteen were unimproved (UI); five others died within 30 days of the operation (D). Follow-up averaged from 12 months (m) in the UI group to 19 m in the I group. Preoperative blood pressures were: C, 179/109 ± 24/12; I, 186/112 ± 35/13; UI, 173/109 ± 49/7; D, 199/114 ± 35/17. The average patient age and preoperative duration of hypertension (HBP) were C, 40.5 years, 33 m; I, 51.5 years, 62 m; UI, 51.5 years, 91 m; and D, 64 years, 92 m. In C group, three patients had serum cholesterol levels > 250 mg%; I, six patients; UI, 11 patients; and D, three patients. Additional signs of atherosclerosis were noted in four patients in C group, in 12 of the I, 13 of UI, and two of D. Intravenous pyelograms done in 49 patients were abnormal in 21 of the 26 patients in groups C and I. In these groups, 18 of 23 radiorenograms were abnormal. Split renal-function tests were always abnormal in the C and I groups (ten tests), but six of eight tests were abnormal in the UI patients. Renal vein renin accurately reflected operative results in all five instances in the C and I groups; peripheral vein renins were less accurate, being normal in four of the C and I groups and abnormal in eight instances. Aortograms were done in 47 patients and all were abnormal. All patients in the C and I groups had abnormal intravenous pyelograms or renograms, hypokalemic alkalosis, bruits, or severe HBP (one young person). The best results were obtained in younger patients in whom HBP had been present for less than five years, cholesterol was less than 250 mg%, and who had little evidence of generalized atherosclerosis.

Palmitic and Oleic Acids as a Major Energy Source for Human Forearm Muscle

Gerald A. Klassen, Montreal, Quebec, Canada, David Rabinowitz,† and Kenneth L. Zierler, Baltimore, Maryland

That plasma free fatty acids (FFA) may be the major fuel for resting muscle was suggested by the facts that forearm glucose uptake accounts for only 15% of O_2 uptake and forearm RQ is 0.75. Because intermuscular adipose tissue delivers FFA to veins simultaneously draining muscle, forearm FFA uptake cannot be measured by arteriovenous (A-V) differences alone. Quantitative measurement of forearm muscle FFA uptake (M) simultaneously with quantitative measurement of forearm adipose tissue FFA output (Q) was accomplished by combining chemical FFA A-V differences with those of radioactive FFA during local intra-arterial infusion of C^{14}-palmitic or C^{14}-oleic acids. For both palmitate and oleate, M approximately equaled Q.

Palmitic acid is 29% of plasma total FFA; M for palmitate accounted for 26% of forearm O_2 uptake. Oleic acid is 40% of plasma total FFA; M for oleate accounted for 36% of forearm O_2 uptake. If extraction ratios (M/arterial input) for the remaining 31% of plasma total FFA are similar to those for palmitate and oleate, then 85 to 90% of forearm O_2 uptake can be accounted for by FFA uptake.

Hemodynamic Implications of Left Ventricular Aneurysm (P)

Michael D. Klein, Francis J. Lane, and Richard Gorlin, Boston, Massachusetts

Total left ventricular end-diastolic volume (LVedv) was determined with thermodilution and angiographic techniques in seven subjects with left ventricular (LV) aneurysms secondary to coronary disease. In five of these cases, the aneurysm formed a large protuberance on the ventricular silhouette; estimates of aneurysm volume were made with correlation between aneurysm size and end-diastolic pressure (LVedp). Aneurysms representing 15 to 30% of total LVedv and containing 75 to 150 ml were accompanied by elevated LVedp of 22 to 29 mm Hg. Smaller aneurysms (< 10 ml) constituting less than 10% of total LVedv were accompanied by normal LVedp. Isoproterenol infusion evoked a marked rise in cardiac (CI) and stroke (SI) indices and mean systolic ejection rate (MSER), and a pronounced fall in LVedp in those cases with elevated LVedv and LVedp at rest. It did not precipitate angina pectoris. Reversion to normal LV function contrasted with the frequent worsening of LV performance in patients with coronary artery disease without ventricular aneurysm. In this latter group, catechol stress, especially when causing angina pectoris, usually produced no change, or an actual increment, in LVedp, and little or no increase in CI and SI and MSER. Striking improvement in LV function with isoproterenol administration suggests replenishment of depleted catechol stores in aneurysmal ventricles. The failing left ventricle involved in aneurysm formation appears uncompensated for by the Frank-Starling mechanism and deficient in that inotropic reserve governed by adrenergic influences. In three patients in whom cardiac oxygen consumption was also measured, isoproterenol markedly increased external mechanical efficiency in two, contrary to the unchanged efficiency resulting in the normal subject.

Effects of Barium Ion on Adult and Embryonic Heart Cells

Morris Kleinfeld and Edward Stein, Brooklyn, New York

Barium chloride was administered to isolated preparations of dog heart and rat atrium and

trypsinized cultured chick heart cells for observation of differences in pharmacological effects. Action potentials recorded through microelectrodes from pacemaker, specialized conductive, and contractile fibers of dog heart and atrial fibers of rat heart showed slowing in the rising and falling phases of action potentials and prominent negative after-potential. Action potentials of the atrioventricular node and Purkinje fibers of dog heart also showed spontaneously progressive diastolic depolarizations. A decrease in resting potential occurred late. Isometric tension output of the right atrium, recorded simultaneously with action potential, showed a significant increase which was more discernible at higher concentrations.

Cultured heart cells were appreciably more sensitive to barium than adult cells. In concentrations as low as 10^{-6}M, the former showed a measurable rise in heart rate. At higher concentrations, there was a pronounced increase in rate, more forceful beating of cells, and induction of beating in previously quiescent cells. Slowing in the rate of rise of action potential is attributed to a decrease in sodium conductance. The slowing of repolarization is due to a decrease in potassium conductance. The marked negative after-potential can be explained on the basis of sustained membrane impermeability to potassium.

The positive inotropic effect on rat atrium is believed due to two mechanisms; one being a membrane effect, while the other is a direct action on contractile processes. The positive chronotropic and inotropic actions of barium on cultured heart cells suggest a close relationship between the actions of barium on adult and embryonic heart cells.

Oxygen Cost of Electrical Activation of the Myocardium

Francis J. Klocke, Eugene Braunwald, and John Ross, Jr., Bethesda, Maryland

Despite many studies on the determinants of myocardial O_2 consumption ($M\dot{V}_{O_2}$), the O_2 requirements of electrical activation of the myocardium have not been defined. Accordingly, nine isolated hearts were perfused with whole blood from which calcium had been removed with an exchange resin and to which disodium ethylenediaminetetraacetate had been added. Spontaneous depolarizations were suppressed by raising the serum potassium to 7 mEq/L, and the right ventricle was stimulated electrically at progressively increasing frequencies. Although these stimuli produced propagated depolarizations, high-sensitivity strain-gauge arches sutured to both ventricles showed no evidence of any associated contractile activity. Changes of $M\dot{V}_{O_2}$ were measured at a constant coronary blood flow and arterial O_2 content by determining changes of venous O_2 content from a continuous recording of venous pO_2. Increases in the frequency of depolarization were accompanied by small but consistent elevations of $M\dot{V}_{O_2}$, averaging 0.38 $\pm$ 0.04 (SEM) μL O_2 per depolarization per 100 g. Similar increases of $M\dot{V}_{O_2}$ occurred in three additional experiments in which the frequency of depolarization was doubled by paired electrical stimulation (PES), suggesting that the altered frequency and rhythm of depolarization in PES cannot account for the marked increase of $M\dot{V}_{O_2}$ which PES produces in the beating heart.

It is concluded that the amount of O_2 required for electrical activation of the heart is less than 1% of the total O_2 consumption of the normally working heart.

Serial Cardiac Output and Blood Volume Studies Following Cardiac Valve Replacement (P)

Frank E. Kloster, J. David Bristow, Albert Starr, Colin W. McCord, and Herbert E. Griswold, Portland, Oregon

Cardiac output (CO) and blood volume (BV) were measured by a radioactive iodine dilution technique in 45 patients having insertion of Starr-Edwards prostheses. Studies were performed preoperatively and sequentially during the first three postoperative weeks. The aortic valve was replaced in 18 patients, the mitral valve in ten, and both valves in eight. Nine patients had triple valve replacement.

CO increased promptly following aortic valve replacement (mean values, 2.5 L/min/m^2 preoperatively; 3.4 L/min/m^2 the second postoperative day). With mitral and double replacement, CO rose more slowly, increasing significantly by the seventh day. Patients undergoing triple replacement had low values preoperatively (mean, 1.6 L/min/m^2). They showed marked improvement by the second day (mean, 2.8 L/min/m^2) and at one week (mean, 3.2 L/min/m^2). CO was normal in all patients except one at the time of discharge.

Three patients with apparently mild tricuspid regurgitation did not have tricuspid replacement. All had persistently low CO the first four days postoperatively (mean, 1.8 L/min/m^2). One has since undergone tricuspid replacement. CO was markedly improved after the second operation, the mean the first four postoperative days being 3.3 L/min/m^2.

BV was decreased in most patients immediately after operation (preoperative mean, 92.1 ml/kg; postoperative mean, 74.0 ml/kg). Low BV was often associated with low CO. Vigorous trans-

fusion resulted in a prompt rise in CO. Patients not transfused showed gradual increases in BV and CO.

CO improves promptly in most patients following valve replacement. Residual valvular lesions or low BV are important causes of persistent low output.

First Derivative of Ventricular Pressure Recorded with Conventional Cardiac Catheters

Thomas J. Knopp, Shahbudin H. Rahimtoola, and H. J. C. Swan, Rochester, Minnesota

Catheter-tip micromanometers permit recording of the first derivative of ventricular pressure pulses (dP/dt), but have inherent disadvantages: zero drift, breakage, valvular or endocardial damage during manipulation, and basic cost. Since dP/dt amplitude is a function of frequency, the first derivative of the strain-gauge output of conventional cardiac catheter systems yields a recording of little value because of artifact distortion.

Open-chest dogs were studied with two manometer systems with resistance-capacitance (RC) differentiating circuits. One used a conventional cardiac catheter with a 15-cycle/sec filter to remove artifact. The other used an 8-cm tube inserted into the left ventricle and connected to a strain gauge (system response uniform to 95 cycles/sec). Pressure pulses recorded with the reference system were submitted to Fourier analysis, and it was found that 95% of the energy components of significance occurred at 15 cycles/sec or less, even for high heart rates. Comparison of dP/dt recorded simultaneously by the two systems indicated a 12% underestimate of peak dP/dt at 2,000 mm Hg/sec, 17% at 3,000 mm Hg/sec, and 25% at 4,000 mm Hg/sec.

It is concluded that conventional catheter systems using RC differentiating circuits and 15-cycle/sec filters provide a satisfactory method for recording dP/dt in human subjects up to a peak dP/dt of 2,000 mm Hg/sec. Moderate errors occur at higher values of peak dP/dt, but directional changes are demonstrated to 7,000 mm Hg/sec. System simplicity, low cost, and applicability to conventional catheter techniques allow routine multiple recordings during diagnostic cardiac catheterization and other hemodynamic studies.

Production of Acute and Chronic Hypertension in Rats by Infusions of Angiotensin (P)

Simon Koletsky, Jose M. Rivera-Velez, and Walter H. Pritchard, Cleveland, Ohio

White male rats were given daily intravenous infusions of synthetic angiotensin. Each infusion lasted up to 12 hours and was repeated for 8 to 12 consecutive days. The dosage rate was 0.01 μg/kg/min, and this yielded hypertensive blood levels. The pressure fell to the preinfusion value when angiotensin was discontinued. Control rats were injected with normal saline according to the same schedule. Animals were assayed for vasoconstrictor material in their circulation by injecting blood from the femoral artery or renal vein into a recipient rat treated with pentolinium tartrate. Assays were made during infusion of angiotensin (acute hypertensive stage) and at intervals of one to four months after the infusions were discontinued (chronic hypertensive stage).

Rats infused with angiotensin for a few days developed acute hypertensive vascular disease indistinguishable from experimental acute renal hypertension. Arterial blood obtained during infusion gave positive assays for vasopressor material. The blood pressures of 15 rats which received from 8 to 12 consecutive daily infusions of angiotensin and of 15 rats which received saline were taken at monthly intervals for four months after the infusions were discontinued. The angiotensin rats showed progressive elevation of blood pressure and became hypertensive by three or four months. In these rats, assays of both arterial and renal venous blood for pressor material were consistently negative. Only 2 of the 15 saline rats became hypertensive.

Thus, temporary infusions of angiotensin into rats over a period of time, followed by complete withdrawal, led subsequently to the development of sustained hypertension. This closely parallels the situation in rats with experimental chronic renal hypertension.

Diuretic Response to Intravenous MK-597

Yi-Hong Kong, George V. Irons, Jr., William M. Ginn, Jr., Glen E. Garrison, and Edward S. Orgain, Durham, North Carolina

Ethacrynic acid (MK-595), recently introduced as a new diuretic agent, has been found effective in refractory edematous states. The cysteine adduct of ethacrynic acid, MK-597, was administered intravenously on 50 occasions to 25 edematous patients in doses of 0.5 mg/kg. Twenty-three of the patients diuresed, losing an average of 1,198 cc over three hours and 2,461 cc over 24 hours, and an average of 1.2 kg in weight. Maximal water, sodium, chloride, and potassium diuresis occurred within the first hour. Although sodium and chloride excretion fell rapidly after three hours, significant potassium excretion continued for 24 hours. Average urinary electrolyte losses during the first three hours were: sodium, 120 mEq/L; chloride, 135 mEq/L; potassium, 24.7 mEq/L; and for the subsequent 21 hours: sodium, 50.6 mEq/L; chloride, 44.6 mEq/L; and

potassium, 41.5 mEq/L. There were no significant alterations in serum electrolyte concentration following a single injection. The drug, administered on 12 occasions to eight patients suffering from acute pulmonary edema, produced marked symptomatic improvement and an average weight loss of 2.0 kg. It proved effective in patients with azotemia (blood urea nitrogen as high as 80 mg%), hypochloremia (chloride as low as 88 mEq/L), hyponatremia (sodium as low as 121 mEq/L), and hypokalemia (potassium as low as 3.4 mEq/L). No significant side effects were encountered. It is concluded that MK-597 is an effective, rapid-acting, diuretic agent suitable for intravenous use in acute pulmonary edema and other edematous states.

Correlation Between the Beta/Alpha-Lipoprotein Ratio and Cineradiographic and Surgically Proven Coronary Atherosclerosis

Robert J. Kositchek, John H. Davis, James A. McEachen, and Rodney T. Smith, Santa Monica, California

Thirty-five patients suspected of having coronary heart disease by clinical history, physical examination, and laboratory data were subjected to selective coronary arteriograms; of these, 14 underwent coronary artery reconstruction or vascular implants. Surgical observations and histological examination of the tissue in each instance revealed the presence of severe atherosclerotic disease, the extent of which correlated well with that revealed by cineangiography. In 8 of the 35, however, cineangiography failed to reveal disease.

Beta/alpha-lipoprotein atherogenic indices were quantitated by paper electrophoresis using Fat Red 7B. Values below 2 were considered negative, those above 2.75 were positive, and intervening values were intermediate for the presence of active atherogenesis.

Of 27 patients designated atherosclerotic by cineradiography and/or surgery, 78% (21 of 27) had lipoprotein values that were distinctly abnormal. In four instances, the index was falsely negative, and in two intermediate values were secured. If the closely related intermediate ratios are classified with the positive values, the correlation between indices and the actual findings would be 85% (23 of 27). Of the eight patients who had no cineangiographic evidence of coronary disease, there was one positive beta/alpha ratio, three that were negative, and four that had intermediate values. Similarly, if the intermediate beta/alpha ratios were classified with the negative values, the correlation of absence of disease with the low beta/alpha ratio would be 88% (seven of eight). There is a close correlation between the lipoprotein ratios and proven coronary atherosclerosis.

Distensibility and Elasticity of the Human Left Ventricle in Diastole

Norman Krasnow, Syed Ahmed, Martin Fox, Richard S. Levine, and Donald N. Summers, Brooklyn, New York

Ventricular diastolic distensibility and elasticity and the role of physiological interventions are relevant to normal and pathological ventricular function, but have not been studied in man. Therefore, cardiac output, ventricular volume (thermodilution method), and simultaneous left atrial and ventricular pressure were measured in 18 subjects with mitral stenosis, thus permitting determination of ventricular inflow (F), volume (V), radius (r), and pressure (P) at 0.04-second intervals of diastole. Curves of distensibility ($\Delta P/\Delta V$), total pressure-volume (P/V), tension-length (T/r, $T = P \times r \times 1{,}332$), and elasticity ($T$ vs. $\Delta r/_r$) at rest were compared with changes after isoproterenol (0.8 to 4.0 μg/min iv), *l*-norepinephrine (12 to 22 μg/min iv), supine leg exercise, and lanatoside C (0.6 to 1.0 mg iv).

P/V and T/r curves were similar, and were generally curvilinear or linear, without stress relaxation. There was no significant alteration in shape of $\Delta P/\Delta V$ in 20 of 24 studies, indicating unchanged distensibility or stiffness ($\Delta T/\Delta r$), regardless of directional shifts in P/V. Elasticity was *linear* up to 16% extension, until late diastole. Its slope (elastic modulus) was unchanged or minimally decreased by isoproterenol (six of seven), exercise (four of five), or lanatoside C (two of two). The only patient with a markedly curvilinear tension-strain curve and *increased* steepness of slope with isoproterenol died at commissurotomy of acute ventricular dilatation.

The data indicate that isoproterenol, *l*-norepinephrine, lanatoside C, and exercise do not alter diastolic distensibility, stiffness, or elasticity. Displacements of P/V or T/r curves are secondary to systolic inotropic effects on the "set" of end-systolic volume and pressure.

Preliminary Study of the Plasma Androgens in Normal Subjects and in Patients with Coronary Artery Disease

Henry S. Kroman, Sheldon R. Bender, and Albert N. Brest, Philadelphia, Pennsylvania

In previous studies, a relationship was observed between the two plasma estrogenic hormones (estrone and 17β-estradiol) and hyperlipemic patients with coronary artery disease. Estrone was observed to be the predominant estro-

gen in the patients with coronary artery disease, while in asymptomatic controls, 17β-estradiol predominated. The purpose of this study was to determine whether differences exist in the concentration of the plasma androgens upon comparing a group of fasting asymptomatic normal men and women and similar groups of patients with coronary artery disease (documented myocardial infarction).

The androgenic hormones (androsterone, etiocholanolone, dehydroepiandrosterone, and testosterone), following their chemical extraction and preliminary column chromatographic purification, were separated and quantitated by gas chromatography. Total cholesterol, triglyceride, phospholipid, and lipoprotein concentrations were determined for each sample by accepted techniques.

Preliminary observations indicate that upon comparing the androgenic hormones in controls with those in patients with coronary artery disease, no significant qualitative or quantitative differences were observed between the two groups. These observations with the plasma androgens, combined with prior results with plasma estrogens, in controls and in coronary artery disease patients, may indicate the existence of an abnormal metabolic pathway leading to the formation of estrogens and not manifesting itself in qualitative or quantitative differences in androgen.

Hemodynamic and Cardiac Metabolic Effects of Mechanical Increase of Vascular Resistance in Experimental Acute Myocardial Infarction with Shock

Leslie A. Kuhn, Howard J. Kline, Robert I. Hamby, Anthony J. Marano, Jr., Lawrence J. Cohn, and Marvin Berger, New York, New York

Various central aortic pressure increments were achieved by partial obstruction of the abdominal aorta with a balloon catheter introduced via a femoral artery. The hemodynamic and cardiac metabolic effects were determined in 28 dogs with acute myocardial infarction and shock produced by plastic-sphere coronary embolization. Alterations of mean central aortic pressure (AP), coronary sinus flow (CF), cardiac output (CO), left atrial pressure (LAP), left ventricular (LV) work, LV O_2 consumption (LV O_2), coronary vascular resistance (CVR), LV mechanical efficiency (ME), and LV lactate and pyruvate extraction were determined before and after coronary embolization and at intervals during one hour of abdominal aortic obstruction.

Following coronary embolization, AP, CO, CVR, and ME declined in all animals, and LV "excess lactate" (XL) appeared in half. With abdominal aortic obstruction, there were significant elevations of postembolic AP, CO, CF, LV O_2, and ME. LAP rose slightly, but not beyond normal levels. Arterial–coronary sinus O_2 difference diminished. LV XL disappeared in half the animals. After one hour of abdominal aortic obstruction, CO, AP, and CF diminished moderately. When AP was maintained at greater than 100% (101 mm Hg) of the postembolic level obtained prior to aortic obstruction, CO, CF, and ME improved to a greater extent, and LV lactate production diminished more than when AP was maintained below this level.

It is concluded that mechanical increase of vascular resistance for periods up to one hour may improve myocardial performance in acute myocardial infarction with shock, and that the increased LV O_2 needs produced are met adequately by the increased CF. This technique may improve the hemodynamic status of patients in cardiogenic shock unresponsive to conventional therapy.

Orthostatic Hypotension as a Clue to Primary Systemic Amyloidosis

Robert A. Kyle, Bruce A. Kottke, and Alexander Schirger, Rochester, Minnesota

Eleven patients with orthostatic hypotension and primary systemic amyloidosis were studied. Dizziness and light-headedness or syncope significantly hampered the involved patients. Three were incapacitated by orthostatic hypotension. Diarrhea, nausea, vomiting, and loss of weight were common, and adrenal insufficiency was seriously considered in the differential diagnosis of 6 of the 11 patients. Abnormal sweating was found in all six in whom this test was done.

The drug, 9-α-fluorohydrocortisone (fludrocortisone acetate), shows promise in symptomatic therapy of the condition. The possibility of primary systemic amyloidosis should be considered in the presence of orthostatic hypotension. Rectal biopsy and bone-marrow aspiration are recommended as initial biopsy procedures unless another organ suitable for biopsy is obviously involved.

Potassium Exchange in Mammalian Ventricular Myocardium (P)

G. A. Langer, New York, New York, and A. J. Brady,† Los Angeles, California

Four phases (0 to 3) were defined kinetically for potassium (using K^{42}) in the dog papillary muscle vascularly perfused for four to five hours with modified Tyrode's perfusate containing 4 mM K^+. Total tissue K^+ after three hours was 41.0 ± 1.06 (SE) mmoles/liter tissue H_2O, and remained stable during the definition of kinetics. The mean rate constant, λ (minutes^{-1}), potassium content (mmoles/liter tissue H_2O), and suggested

origin of each phase are, respectively: (0) $\lambda_0 =$ 3.2, 0.3, vascular; (1) $\lambda_1 = 0.65$, 2.06, interstitial; (2) $\lambda_2 = 0.0139$, 39.3, intracellular; (3) $\lambda_3 <$ $0.004, < 0.5$, ? origin.

Alteration of K^+ concentration of perfusate (0 and 16 mM) produced significant changes in the intracellular exchange rate of K^+. This was in marked contrast with increments in frequency of contraction which had no effect on the over-all exchangeability of intracellular potassium. Increases in rate were, however, associated with a transient net loss of intracellular K^+. This loss continued if active tension declined and contracture progressed in the muscle, but ceased if muscle function remained stable in the face of continued increased frequency of contraction. A positive tension staircase was approximately proportional to the net K^+ loss. The net K^+ loss was 0.93 mmoles/liter tissue H_2O in nine muscles in which a mean 27 beat/min rate increment was introduced for 16 minutes. This represented 2.3% of intracellular K^+. There was a significant time lag before the net K^+ loss reached a maximum rate and began to decline. The K^+ movements are consistent with the theory that Na^+ movements into and out of the cell are possibly related to Ca^{++} movements and thereby contribute to control of myocardial contractility.

Evoked Cortical Potentials in Patients with Stroke (P)

Sanford J. Larson, Anthony Sances, Jr., and John B. Baker, Milwaukee, Wisconsin

Evoked cortical potentials secondary to peripheral electrical stimulation were recorded using scalp electrodes in patients with stroke. Stimulating electrode pairs were applied bilaterally to the wrists, and rectangular pulses of 0.3-msec duration delivered by a current stimulator. The scalp electrodes were applied bilaterally, 3 cm from the midline, at a point halfway between the nasion and inion, and 8 cm anterior to this point. The signals picked up by the scalp electrodes were amplified by a high-rejection-ratio, low-level preamplifier and fed into a data-retrieval computer. To insure reproducible conditions, the positions of stimulating and recording electrodes were measured relative to fixed external landmarks, and the stimulating current recorded.

Ten patients with decreased sensory perception following a stroke have been studied with this technique. Three patients had clinical and arteriographic observations suggestive of a thalamic lesion. A short latency-evoked response was obtained from the normal side of the brain only with contralateral stimulation. On the affected side, the response was obtained only with ipsilateral stimulation, indicating conduction over the corpus callosum and confirming the thalamic location of the lesion. In seven cases, responses could be recorded only from the normal side with contralateral stimulation, suggesting involvement of the sensory cortex.

Development of a Simple Surgical Procedure for Coronary Artery Disease (P)

Banning G. Lary, John G. Chesney, and Thomas O. Gentsch, Miami, Florida

Studies in over 150 dogs have led to the development of a simple and rapid procedure for coronary artery obstruction and stenosis. This procedure has been performed in one human without operative incident and the early results are excellent. Initial work showed that an autogenous vein could be approximated to the epicardium, which had been reflected longitudinally from the coronary artery. After the needle holes were sealed by repeated injections of blood, a common lumen was created between the artery and the vein, and this "neolumen" was initially kept open by intra-arterial heparin administration just proximal to the new vessel. Concepts gained in this work were extended to a new operation in which the visceral surface of the artery was cut longitudinally a short distance into the myocardium. A new vessel was formed which consisted of the previous arterial wall (one-third) and the myocardium (two-thirds). Finally, a special automatic scalpel was developed and, working through the marginal artery, a 1-mm stenosis of the right coronary artery of a human was surgically attacked. No occlusion occurred from this operation and all symptoms of angina are absent.

Chronic, Advanced Left-Heart Failure in Dogs

Richard P. Lasser, Jacob I. Haft, Bertram J. Newman, Douglas F. Allen, John Ishigura, and Charles K. Friedberg, New York, New York

Chronic, advanced, left-heart failure was produced in nine dogs by creating two cardiac lesions, that is, a shunt between the subclavian artery and left atrium and a myocardial infarction induced by coronary arterial ligation. Cardiac catheterizations and systemic blood flow determinations (Fick) were performed preoperatively and postoperatively under chloralose-urethan anesthesia. Six animals were studied postoperatively during exercise (electrically induced muscular contraction), two during administration of angiotensin II, and four with measurements of creatinine (Ccr) and para-aminohippurate (Cpah) clearances.

Results demonstrated that left ventricular end-diastolic pressure (LVEDP) had risen from an average preoperative value of 5.2 mm Hg to 20.6 mm Hg, average systemic blood flow had declined

from 3,333 ml/min to 2,575 ml/min, while right ventricular end-diastolic pressure had declined slightly from 5.1 mm Hg to 3.6 mm Hg. Ccr and Cpah had not altered from preoperative levels. Moderate exercise (oxygen consumption rising from 138 ml/min to 473 ml/min) produced a rise in LVEDP in all postoperative animals (average 7.1 mm Hg), concomitant with an increase in systemic blood flow. Normal animals, similarly studied, showed slight declines in LVEDP but a comparable increase in systemic flow. Synthetic angiotensin caused dramatic rises in LVEDP.

Five dogs died in pulmonary edema on the first, twelfth, thirteenth, fifteenth, and twentieth postoperative day, respectively. A ventricular aneurysm had developed in two. Four dogs have survived for several months. No peripheral edema or ascites were observed in any animal.

Thus, chronic, advanced left ventricular failure has been produced in dogs. Despite hemodynamic abnormalities of the left heart, no evidence was obtained of grossly abnormal salt and water retention.

Two-Dimensional Nomogram for Normal and Abnormal Blood Pressure in the Aged

Richard P. Lasser and Arthur M. Master, New York, New York

The purpose of this communication is to introduce a method for comprehensive analysis of normal and abnormal systolic and diastolic pressures in the aged and synthesis into a single nomogram. "Normal" subjects consisted of 5,750 persons, aged 65 years and over, who were apparently healthy and ambulatory. The "abnormal" subjects consisted of 1,189 men and women who had hypertensive cardiovascular disease on the basis of electrocardiographic abnormalities, cardiac enlargement, or involvement of the cerebrovascular system or kidneys, in addition to elevated blood pressure. The "normal" and "abnormal" groups were divided by sex. Scattergrams were constructed of the distribution of systolic (abscissa) and diastolic (ordinate) pressures. Regression lines were then calculated for each group and both sexes to express the relationship of diastolic pressure (D) to all levels of systolic pressure (S). The equations were: normal males, $D = 0.340S + 32.44$; females, $D = 0.292S + 38.85$; hypertensive males, $D = 0.242S + 53.26$; females, $D = 0.273S + 45.18$. Discriminant function analysis between the normal and abnormal was then performed, providing a line of best separation between the two, and dealing simultaneously with systolic and diastolic pressures. To further characterize the two "universes," central contour ellipses were calculated for each. From the correlation of this material, a nomogram was constructed showing the simultaneous distribution of systolic and diastolic pressures, both normal and abnormal, in the aged, as well as the lines of best separation. This kind of analysis affords a comprehensive approach to problems in blood pressure.

Factors Affecting Survival in 100 Paced Patients with Complete Heart Block

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Indications for pacing in 100 paced patients with complete heart block were (1) the presence of Stokes-Adams attacks and (2) the occasional presence of congestive heart failure. Immediate mortality and short-term follow-up were compared with a controlled group of 50 patients studied before pacing became available. The unpaced and paced series were divisible into those with chronic complete block or changing block (two-thirds) and those with acute temporary block (one-third) in acute myocardial infarction. The following factors were found to have significant effects, both singly and in combination, on the prognosis in complete heart block: (1) cardiac complications —failure, infarction, shock, Stokes-Adams attacks; (2) extracardiac complications, such as diabetes, uremia, and a cerebrovascular accident; and (3) miscellaneous complications—bronchopneumonia, embolism, septicemia, carcinoma. Factors having the greatest effect on mortality were acute myocardial infarction, diabetes, uremia, shock, Stokes-Adams attacks, and a ventricular rate below 30. Various electrocardiographic features, such as changing block and duration of the QRS interval, had no effect on mortality. The prognosis in chronic complete block was improved materially by pacing, although prognosis depended on the frequency and severity of cardiorenal or metabolic complications However, reduction in mortality with pacing in the temporary block of acute myocardial infarction was minimal.

Unique Diagnosis of Primary Aldosteronism by Aldosterone "Suppression" Testing

David P. Lauler, Paul I. Jagger, Anthony I. Vagnucci, and George W. Thorn, Boston, Massachusetts

The diagnosis of primary aldosteronism due to either an adrenal adenoma or bilateral adrenal hyperplasia traditionally has required prolonged metabolic balance studies. The "suppression" testing procedure is based on the cardinal feature of primary aldosteronism, namely, an inability to

suppress the basal aldosterone secretion rate during salt-loading. This inability to suppress is due to autonomous aldosterone production. Patients with primary aldosteronism are able to increase their aldosterone secretion in response to salt deprivation; hence, this latter procedure has little clinical utility.

To standardize the aldosterone "suppression" testing, five normal subjects, five patients with edema due to secondary aldosteronism, and two patients with primary aldosteronism were placed on a constant 200 mEq sodium intake for a five-day period. Normal subjects "suppressed" their control aldosterone secretory rates (ASR) from levels of 100 to 250 μg/day to values of less than 50 μg/day and rapidly achieved salt balance. Patients with secondary aldosteronism failed to suppress their control ASR and did not achieve sodium balance but, rather, went into positive sodium balance. The two patients with primary aldosteronism had elevated control ASR (400 to 600 μg/day) and failed to suppress on the five-day period of salt-loading, yet rapidly achieved sodium balance. This inability to suppress an elevated level of aldosterone secretion by salt-loading coupled with the ability to achieve sodium balance is unique for the diagnosis of primary aldosteronism.

"Rebound" Aldosteronism: Practical Aspects in Diuretic Therapy (P)

David P. Lauler, George L. Pauk, Anthony I. Vagnucci, and George W. Thorn, Boston, Massachusetts

Following a vigorous diuretic program in patients with edema disorders, a period of profound sodium retention often occurs. This postdiuretic period of sodium retention usually offsets the prior benefits of the diuretic therapy. Clinical studies were designed to elucidate the mechanism of this postdiuretic sodium-retaining state.

Normal subjects and patients with either congestive heart failure, nephrosis, or cirrhosis were admitted to our metabolic unit and placed on constant diet, urinary collections, and activity. Dietary sodium intake was fixed at either 200 mEq (high) or 10 mEq (low) of sodium. Complete electrolyte balance studies were carried out. Aldosterone secretion rates (ASR, double-isotope method) were determined the day prior to (control), the day of, and the day after diuretic (ethacrynic acid) administration. Ten studies were performed. In normal subjects on high salt intake, diuretic volume depletion caused only a modest increment in ASR, whereas on a low sodium intake a more marked increment in ASR occurred. For example, subject Rh. on high salt intake increased ASR from 46 (control) to 135 μg/day after a single day of diuretic therapy, while on low salt intake the subject increased ASR from 418 to 2,101 μg with comparable diuretic responses. Comparable results were seen in patients with edema disorders, except that the basal levels of ASR were higher. It is concluded that during diuretic therapy and immediately thereafter, a marked increment in ASR occurs which is related to the degree of volume depletion induced. This "rebound" aldosteronism is exaggerated by salt or fluid restriction.

Serum Cholesterol Values in Veterans with Myocardial or Cerebral Infarction: Report of the Veterans Administration Cooperative Study of Atherosclerosis, Neurology and Cardiology Sections (P)

Joseph E. LeBauer, Samuel J. Friedberg,† Albert Heyman, Durham, North Carolina, and Julian Lewis, Washington, District of Columbia

A study was made of the level of serum cholesterol in 771 men in 39 Veterans Administration hospitals who had recent episodes of atherosclerotic occlusion in either the coronary or cerebral arteries. Myocardial infarction was present in 367 patients and cerebral infarction in 404 others. The diagnosis of either cerebral or myocardial infarction was based on previously defined clinical and laboratory criteria, the patients comprising part of a nation-wide VA cooperative study of therapy of atherosclerosis. Blood samples for cholesterol determinations were taken approximately two months after discharge from the hospital and prior to treatment with estrogenic agents or cholesterol-lowering medications. All determinations of serum cholesterol were made in the VA Central Lipid Laboratory; care was taken to maintain precise laboratory standards.

Patients with myocardial infarction in the fourth and fifth decades of life had mean serum cholesterol values of 238 mg% and 251 mg%, respectively, values appreciably greater than the 216 mg% and 237 mg% found in patients of comparable ages with cerebral infarction. In the sixth age decade the mean serum cholesterol values in patients with either cerebral infarction or myocardial infarction were approximately the same (237 and 239 mg%). After the sixth decade patients with cerebral infarction tended to have a higher mean cholesterol level than those with myocardial infarction, with values of 240 and 227 mg%, respectively.

The level of serum cholesterol appears to correlate with the known age distribution of vascular occlusive disease in the heart and brain. Myocardial infarction occurs more frequently in younger age groups, at which time their serum cholesterol level is elevated. Cerebral infarction, on the other

hand, is more frequent at older ages and is then associated with a higher serum cholesterol than is present in patients of comparable age with myocardial infarction.

Vasoactive Drugs in Cardiac Diagnosis

Marion K. Ledbetter, Jackson T. Paden, Maria M. Torres, and James M. Shultz, Tulsa, Oklahoma

During right- and left-heart catheterization of 19 subjects, eight with normal hearts and 11 with variable-sized ventricular septal defects, circulatory dynamics were altered by drugs to evaluate better the functional state of the myocardium and pulmonary vascular bed. All were sedated with meperidine, chlorpromazine, and promethazine hydrochloride.

After control studies without medication, as separate studies dilute solutions of norepinephrine and isoproterenol were infused into the pulmonary circulation until nearly maximal cardiovascular responses were obtained. The electrocardiogram and pulmonary and aortic pressures were recorded continuously. Indicator-dilution curves were recorded after sudden injections of indocyanine-green dye into a distal pulmonary artery with sampling from the aorta and, when feasible, simultaneously from the main pulmonary artery.

Responses were, in general, similar in the two groups. Both norepinephrine and isoproterenol exerted positive inotropic effects on the heart. Whereas norepinephrine caused reflex bradycardia, increased systemic and pulmonary resistance, and prolonged circulation times, isoproterenol caused tachycardia, decreased circulatory resistance, and decreased circulation times. The net effect on cardiac output of norepinephrine was nil or slight in either direction; the effect of isoproterenol was invariably a significant rise.

Shunts were quantitated by oxygen saturation and dilution curve methods. Norepinephrine augmented and isoproterenol diminished left-to-right shunting. In the only two patients with severe pulmonary hypertension, norepinephrine increased left-to-right and decreased right-to-left shunting, indicating greater reactivity in the systemic than in the pulmonary vascular bed.

These stress responses aided in selection of patients for or exclusion from surgical considerations.

Physiological Alterations of the Function of the Heart by the Application of Alternating Electrical Current of Various Frequencies: New Method for Slowing the Heart and Potentiating Systolic Contraction (P)

Armand A. Lefemine, Boston, Massachusetts

The favorable alteration of function of the heart by electrical current has significant practical implications. Investigations on the effect of alternating current, using frequencies of 5, 10, 20, and 1,000 cycles/sec, applied directly to the surface of the heart revealed that alternating current can be used safely in the range of 5 to 10 and 1,000 cycles/sec. Two consistent effects were noted: (1) The heart rate was reduced by one-half, and (2) the pulse pressure was doubled by elevation of the systolic level. Heart rates varied from 140 to 250 per minute. Pulse pressure increases varied from 20 to 65 mm Hg and averaged 46 mm Hg.

These physiological effects can be produced by continuous or intermittent application of electrical energy at these frequencies. Synchronization of a short burst of the electrical current (0.3 sec) with the R wave of the electrocardiogram or the pulse pressure wave produces the same deceleration effect. Current investigations utilizing intracardiac electrodes and external skin electrodes reveal that the same effects can be produced without thoracotomy, although not with the same consistency. The pulse pressure changes that have been observed are similar to those produced by postextrasystolic potentiation.

Protection Against Cardiovascular Collapse Following Acute Adrenalectomy by Prior Adrenal Denervation (P)

Allan M. Lefer and William F. Burnett, Charlottesville, Virginia

Removal of both adrenals in a one-stage operation in eight dogs resulted in a state of cardiovascular collapse within two hours in all animals. This state was characterized by a $51.8 \pm 3.8\%$ reduction (46 to 22 g) in left ventricular contractile force (LVCF), a $59.2 \pm 3.4\%$ drop (131 to 53 mm Hg) in mean arterial blood pressure (MABP), a $36.8 \pm 4.5\%$ fall (239 to 151 ml/min) in femoral blood flow (FBF), and a $20.2 \pm 5.9\%$ increase (148 to 178) in heart rate (HR). Adrenal denervation (splanchnicectomy) 14 days prior to adrenalectomy prevented the cardiovascular collapse in eight of eight dogs. No significant changes (less than 10%) were observed in LVCF, MABP, FBF, and HR. Sham denervation provided no protection in two dogs. These animals responded similarly to the nontreated dogs. Plasma corticosteroid levels (Porter-Silber method) fell to undetectable levels one hour after adrenalectomy in all groups. The data suggest that adrenocortical insufficiency alone is not the primary cause of the cardiovascular collapse which occurs soon after acute bilateral adrenalectomy. Increased activity of the sympathetic nervous system in the face of very low corticosteroid levels may be a major precipitating factor.

Sounds of Mild Mitral Regurgitation: Observations from Intracardiac Phonocardiograms and Pharmacological Responses

Richard F. Leighton, St. Petersburg, Florida, William L. Page, Sarasota, Florida, Richard S. Goodwin, Charles F. Wooley, and Joseph M. Ryan, Columbus, Ohio

Mild mitral regurgitation was diagnosed in 15 patients, aged 17 to 48, each with a well-localized apical systolic murmur and no electrocardiographic or radiological evidence of left atrial or ventricular enlargement.

Phonocardiograms were recorded in the left heart by a transseptal technique in 12. The typical murmur of high frequency and low intensity was recorded in the mitral valve area at each attempt, three times after intravenous phenylephrine infusion. It was seen to undergo transition from pansystolic to entirely late systolic as the recording device was progressively withdrawn from an apparently well-localized regurgitant jet, suggesting a positional mechanism for similar changes in murmur configuration noted externally.

Recordings in 12 patients were made in the esophagus at the atrial level where a murmur was usually audible after phenylephrine and in the right heart where no murmur was evident. All had external phonocardiograms with pharmacological studies. Following amyl nitrite inhalation the early murmur component increased, while the late component decreased. The latter was intensified by phenylephrine. All had normal right-heart catheterizations with exercise studies in eight. Confirmatory left ventricular angiograms were obtained in nine.

Three patients had late systolic clicks, and two had systolic whoops. The recording of these sounds within the left heart and their responses to drugs suggest they emanate from the mitral valve during regurgitation. Etiology remains uncertain in the majority. Cerebral embolization (once) and significant arrhythmias (twice) in three older patients constitute additional risks of this entity, generally considered benign.

Anatomical Base of a Case of Wolff-Parkinson-White Syndrome Terminating in Complete Atrioventricular Block (P)

Maurice Lev, Chicago, Illinois, William B. Leffler, Marion, Ohio, Richard Langendorf, and Alfred Pick, Chicago, Illinois

A 34-year-old male was found to have Wolff-Parkinson-White syndrome in 1952 and 2:1 block in 1955. In 1957 he died in complete atrioventricular (A-V) block during an Adams-Stokes attack.

The A-V rings and the conduction system, serially sectioned for a total of 14,662 sections, revealed an abnormality in the formation of the fibrous skeleton of the heart. The tricuspid annulus made no connection with the trigonum fibrosum dexter, only with the pars membranacea. A fasciculus of muscle fibers passed from the atrial septum through the mitral annulus to the beginning of the A-V bundle, bypassing the node. Large fasciculi of Mahaim fibers then proceeded from the A-V bundle to the ventricular septum. A degenerative disease of the myocardium had severely involved the approaches to the node, the periphery of the node, the penetrating and branching portions of the A-V bundle, the Mahaim fibers to the septum, and the left and right bundle branches. This was superimposed on marked fibrosis of the right and left bundle branches. No bundle of Kent was found.

This is considered to be a case of pre-excitation, with bypass of the node, with functional Mahaim fibers transmitting the impulse to the septum. The secondary degeneration of the approaches to the node, of the penetrating bundle, and of Mahaim fibers destroyed this bypass tract. The degeneration and fibrosis of the bundle and bundle branches produced A-V block. This is the first presumed clinical demonstration that Mahaim fibers may conduct.

Intravenous *d*-Aldosterone in Man

Daniel M. Levin and Robert Cade, Gainesville, Florida

Availability of *d*-aldosterone for clinical use makes it important to know its effects in various disease states. Accordingly, 500 to 1,000 μg *d*-aldosterone were acutely administered intravenously to one normal subject, one patient with cirrhosis and ascites, one with secondary hyperaldosteronism, three with mild to moderate hypertension, and three with renal failure and secondary heart disease. All were maintained on a constant diet and fluid intake. The most consistent effects were reductions in urinary sodium and sodium-potassium ratio, which occurred in eight; they increased in the one patient with cirrhosis. Urinary ammonia rose in seven and declined in two; titratable acidity increased in five of eight; as a result, urinary pH fell in six of eight. Potassium excretion increased in seven of nine; urinary calcium and magnesium decreased in six of nine. Urinary phosphate rose in five, declined in two, and was unchanged in two; chloride excretion decreased in four of six cases. Creatinine clearance fell insignificantly in seven of eight subjects. Urinary sulfate and flow showed no consistent changes; urinary osmolality reflected changes in urinary volumes. Serum electrolytes, pH, osmol-

ality, creatinine, and hematocrit showed no consistent or significant changes. Maximal reduction in urinary sodium, calcium, and magnesium occurred four to six hours after intravenous *d*-aldosterone, whereas the peak increase in potassium, ammonia, titratable acidity, and phosphate excretion occurred after eight to 12 hours. These results indicate that patients with these disease states, except cirrhosis with ascites, respond in the same way as normal individuals to intravenous *d*-aldosterone.

Relative Pulmonic Insufficiency: Critical Appraisal by Intracardiac Phonocardiography and Pulmonic Valvulography

Hugh S. Levin, Vincent Runco, and Richard W. Booth, Omaha, Nebraska

Although most patients with mitral stenosis and a basal diastolic murmur have aortic regurgitation, a direct critical appraisal of relative pulmonic insufficiency in rheumatic heart disease is conspicuously lacking.

In order to assess the true incidence of the Graham Steell murmur, 24 patients with mitral stenosis and the usually accepted criteria for relative pulmonic insufficiency were studied. In addition to right- and left-heart catheterization, the competency of the pulmonic valve was evaluated by intracardiac phonocardiography and a new cineangiographic method for pulmonary valvulography which obviates false insufficiency from catheter-induced valve distortion. The validity of intracardiac phonocardiography was established in normal dogs. Consistent detection of significant regurgitant murmurs in the right ventricular outflow tract correlated with the cineangiographic demonstration of pulmonic insufficiency when pulmonary valve distortion was produced by a second catheter. Aortic regurgitation was evaluated by retrograde valvulography.

Objective evidence of pulmonic insufficiency was found in only one of the 24 patients, and this was demonstrated by both techniques. Aortic regurgitation was present in 23, including the patient with pulmonic insufficiency. Unusual transmission of the mitral stenosis murmur was misinterpreted as semilunar valve incompetence in one case.

These studies (1) validate the reliability of intracardiac phonocardiography and the unreliability of transvalvular pulmonic valvulography in the evaluation of pulmonic insufficiency, (2) confirm the rare existence of pulmonic insufficiency in rheumatic heart disease, and (3) further implicate aortic regurgitation as the usual source of basal diastolic murmurs associated with mitral stenosis.

Blood Sludging Observed at the Bedside: Feasibility and Limitations of Examination by Ophthalmoscopy

Harold D. Levine and Roe E. Wells, Boston, Massachusetts

The bulk of the literature on intravascular erythrocyte aggregation, "sludging," has been based on observations made by photomicrographic techniques. It has recently become clear that this same phenomenon may be observed with the plus 40 lens of the ophthalmoscope, which technique offers the advantage of easy and inexpensive serial bedside observations. A series of over 200 patients with cardiovascular disease has been observed by this method, and the observations were correlated with photomicrographs using the same relative magnification. The majority of observations have been made in patients with angina pectoris and/or myocardial infarction. Control observations have been made in healthy subjects of equivalent ages.

The most marked examples of this phenomenon were seen in acute myocardial infarction. The degree of sludging generally became less pronounced or disappeared during the recovery process. Sludging was not observed in a few cases studied at the very onset of the illness but became pronounced shortly afterwards. In a few subjects with infarction, phlebotomy, which effectively lowered an elevated hematocrit, did not eliminate the sludging. The technique has also been useful in following the patient suspected of thromboembolic disease. In many of these patients, sludging was observed at a time when the diagnosis was considered but not established. Sludging may also alert the clinician to the presence of organic disease in the neurotic patient. While the sludging process is a nonspecific abnormality, it does have great advantage when followed serially in the same patient who serves, as it were, as his own control.

Effect of Exercise on the Cardiopulmonary Blood Volume in Man

Gilbert E. Levinson, Albert D. Pacifico, and Martin J. Frank, Jersey City, New Jersey

The volume of blood in the heart and lungs has been reported by different workers to increase, decrease, or be unchanged by exercise. These disparate results arise chiefly from the measurement by indicator-dilution studies of "central" volumes which, because of their temporal boundaries, are not estimates of the true cardiopulmonary blood volume (CPBV). To settle this question, mean transit time volumes from right atrium to aortic root were measured from indocyanine-green dilution curves in 11 normal human subjects at supine

rest, with elevation of the legs to bicycle pedals, and during supine bicycle exercise. At rest, with mean cardiac index of 3.1 L/min/m^2, oxygen consumption 120 ml/min/m^2, heart rate 75 beats/min, and stroke volume index 42 ml/m^2, CPBV was 412 ml/m^2 or 15% of estimated total blood volume. Reproducibility of volume measurement was good, the mean coefficient of variation for 33 measurements at rest being 3.7%. With leg elevation for 20 minutes, CPBV rose in all but one subject, the mean increase being small (6.4% of resting value) but statistically significant ($P < 0.05$), while no change occurred in output, rate, or stroke volume. During 20 minutes of moderate exercise, with two- to threefold increases in oxygen consumption, there was no further change in CPBV, despite significant ($P < 0.005$) mean increases in output (1.93 L/min/m^2), rate (35 beats/min), and stroke volume (4.5 ml/m^2). It is concluded that except for the small increase attributable to leg elevation in supine subjects, the CPBV in normal man is not altered by exercise.

Prediction of Left Ventricular End-Diastolic Volume from a Peripheral Arterial Indicator-Dilution Curve

Richard P. Lewis, J. David Bristow, and Herbert E. Griswold, Portland, Oregon

Indocyanine-green dilution curves from left-heart injection and brachial arterial sampling were obtained during thermodilution measurement of left ventricular end-diastolic volume (LVEDV) in 71 patients with various cardiac lesions. No patient had mitral regurgitation. Exercise measurements were also made in 23 patients. Peak concentration/slope time ratios (PC/ST) were calculated from the dye curves by the method of Jose et al. The indicator dose is corrected for body size in this calculation. PC is decreased and ST prolonged by an increase in dilution volume. PC/ST will thus be lowered by an increase in dilution volume. PC/ST values ranged from 2 to 90, and LVEDV ranged from 67 to 422 ml/m^2 (upper limit of normal 135 ml/m^2). When PC/ST was 25 or less, LVEDV was elevated in 46 of 50 instances. When PC/ST was greater than 25, LVEDV was normal in 43 of 44 instances. This relationship was unaffected by cardiac output. The highest PC/ST values occurred in patients with the lowest LVEDV values. When the left atrium (LA) was grossly enlarged but LVEDV normal (mitral stenosis), the PC/ST from a LA injection was considerably lower than from the LV. There was no significant difference between the two curves when the LA was not greatly enlarged (aortic valve disease). Thus, a PC/ST of more than 25 from either an LA or LV injection is a simple and reliable method of establishing a normal LVEDV.

Differentiation of Aortic-Valvular Stenosis from Subaortic Muscular Stenosis by Timing the Arterial Sounds

Albert J. Libanoff and Simon Rodbard, Duarte, California

An innocuous means for differentiation of aortic valvular stenosis from subaortic muscular stenosis is reported. The arterial sounds of sphygmomanometry were recorded by microphone and displayed on a two-channel recorder simultaneously with a reference electrocardiogram. The falling cuff pressure level was noted at 10-mm Hg intervals by the introduction of standardization impulses into the electrocardiographic tracing. The cuff pressure of each beat was plotted against the time from the onset of each QRS complex (Q) to the onset of the following arterial sound (K). In five patients with aortic valvular stenosis, the QK at both systolic and diastolic pressures was delayed in proportion to the pressure gradient across the aortic valve determined at cardiac catheterization. By contrast, QK values were early in six patients with subaortic muscular stenosis. The mechanism in aortic valvular stenosis is apparently primarily dependent on the obstruction offered to ejection by the stenotic valve. In subaortic muscular stenosis there is no obstruction early in systole, and the early ejection takes place without impedance.

Acute Pulmonary Vascular Congestion due to Ectopic Ventricular Beats

Albert J. Libanoff and Simon Rodbard, Duarte, California

Catheterization data on 20 patients demonstrate that an episode of ventricular arrhythmia may result in an acute elevation of pulmonary blood pressure. In regular ventricular rhythms, left and right ventricular outputs are equal, and pulmonary vascular blood volume remains relatively constant. This pattern is disturbed in ectopic arrhythmias such as occur in the course of ventricular beats generated by an intraventricular catheter. An ectopic beat results in an ineffective left ventricular contraction which is inadequate to open the aortic valves and produce ejection; a systemic pulse deficit results. Catheterization data show that a systemic pulse deficit is seldom accompanied by a pulmonary arterial pulse deficit because the limited force generated by the right ventricle is sufficient to eject blood into a pulmonary artery in which the pressure is at normal or only slightly elevated values. A succession of such ectopic beats leads to a progressive

input into the pulmonary vascular bed, increasing the pulmonary arterial and left atrial pressures and resulting in pulmonary congestion. In decompensated patients the high left atrial pressure can rise quickly to values at which acute pulmonary edema may result. This sequence may explain the occurrence of acute failure and sudden death, usually ascribed to coronary occlusion, in patients with cardiac decompensation.

Elective Termination of Anticoagulation in Coronary Artery Disease

Jerrold S. Lieberman and Marianne Lindner, New York, New York

The New York Hospital experience with 125 patients observed for 325 patient years indicates that anticoagulants may be withdrawn from selected patients with coronary artery disease without subsequent increase in mortality, providing the withdrawal is gradual.

The data pertain to 125 patients with coronary artery disease who were treated in the Anticoagulant Clinic during the period 1960 to 1964: 108 for myocardial infarction and 17 for coronary insufficiency. There were 18 deaths during 236 patient years of anticoagulation and six deaths during 88 patient years following termination of anticoagulants.

Fifty-five patients were selected for elective termination. They were mainly between the ages of 50 and 70 with a history of a single myocardial infarction. A history of angina was present in 64% (35 of 55). Coumarin drugs were withdrawn gradually over a period of nine weeks. Following withdrawal, patients were observed for a total of 71 patient years. One patient died four months after termination, and two others had nonfatal myocardial infarctions. The adjusted mortality rate was 1.4% per year.

Termination was abrupt in 19 patients. There was no immediate mortality, but four patients died between the fifth week and the sixth month thereafter. During the year following termination, there were 11.4 patient years of observation and an adjusted mortality rate of 35.8%.

The difference in mortality rates between gradual and abrupt termination of anticoagulation was highly significant statistically ($P < 0.01$).

Role of Hemodilution and Phenoxybenzamine (Dibenzyline) in Prevention of Renal Ischemia During Cardiopulmonary Bypass

C. Walton Lillehei, Robert L. Simmons, Ira D. Miller, and Raymond C. Bonnabeau, Jr., Minneapolis, Minnesota

Diminished renal blood flow, increased circulating catecholamines, and hemolysis act synergistically in producing renal failure. In order to study the deleterious conditions affecting renal circulation during cardiopulmonary bypass, an arteriographic in vivo technique has been developed. Noteworthy effects on renal circulation were produced by such factors as hemodilution, *l*-norepinephrine, cortisone, phenoxybenzamine, Rheomacrodex, 5% glucose in water, and reserpine.

Renal arteriograms in 100 adult mongrel dogs divided into control and study groups were sequentially studied every 30 minutes during two hours of total cardiopulmonary bypass with the bubble oxygenator at normal temperature and constant flow rate. Initial priming volume of 20 ml/kg body weight was used for hemodilution. A comparison between fresh heparinized homologous blood, Rheomacrodex, and 5% dextrose in water revealed marked renal artery constriction and larger priming volumes for constant flow when dextrose in water was used. Treating animals with cortisone or infusion of norepinephrine caused extreme renal artery constriction. Phenoxybenzamine completely reversed the ischemic pattern in each of these cases.

These studies indicated that renal perfusion can be improved in prolonged extracorporeal circulation by the use of phenoxybenzamine as an adrenergic blocking agent.

Theory of Atrioventricular Block: Explanation of Supernormal Conduction and Varying Block

Arthur J. Linenthal and Paul M. Zoll, Boston, Massachusetts

Quantitative studies of electrical stimulation of the ventricles in patients with atrioventricular (A-V) block have disclosed (1) a new shape to the curve of ventricular excitabilty in diastole and (2) strong evidence that sinoatrial impulses in A-V block are conducted decrementally.

The effectiveness of stimuli of varying amplitudes was studied at intervals after a preceding ventricular beat. A period of supernormal excitability just after the refractory phase was observed during which the threshold was lower than in the next period, the "normal" diastolic phase. Then, stimuli that were ineffective in early diastole became effective later; i.e., contrary to the classic concept of a constant diastolic level, the threshold falls progressively. Consequently, depending on their rates, successive stimuli produced various patterns of response, such as 1:1, 2:1, and 3:1.

Seemingly haphazard variations in conduction assumed orderliness and meaning when interpreted in the light of a theory of A-V block developed from our observations on ventricular excitability and similar to Erlanger's hypothesis in 1906: In A-V block sinoatrial impulses undergo decre-

ment and reach the ventricles at intensities near threshold levels; ventricular response to the atrial impulses depends on their intensity and their timing on the excitability curve. Conducted beats occurred in two zones, corresponding to the early supernormal and the late rise in excitability, with block in between. The varying patterns of A-V block are analogous to the patterns of response to ventricular stimuli that we observed; marginal atrial impulses may be conducted late in diastole, even though blocked earlier. "Complete" or "partial" A-V block, "A-V dissociation," and "supernormal conduction" can readily be explained by this theory.

Late Apical Systolic Murmur: Clinical, Hemodynamic, and Angiographic Data in Seven Patients

Joseph W. Linhart and W. Jape Taylor, Gainesville, Florida

The late apical crescendo systolic murmur generally has been considered to be an innocent murmur or to be associated with a benign form of acquired mitral regurgitation. Hemodynamic and angiographic data have been obtained in six of seven patients with this characteristic murmur. Left ventricular cineangiography demonstrated a ballooning deformity of the mitral valve with overhanging of the valve insertions during systole, producing delayed mitral regurgitation in each patient (grades I to III of IV). Six were females with an age range of 22 to 43. In five patients the murmur was first heard at an early age (7, 9, 10, 14, and 18 years); only two gave a history of rheumatic fever. Paroxysmal arrhythmias were a prominent symptom in five; all were clinically class I or II. Left ventricular hypertrophy was documented by electrocardiogram and vectorcardiogram in two patients with radiographic signs of left ventricular and atrial enlargement. Normal pulmonary artery and left atrial pressures, pulse contours, and cardiac indices were present in all subjects. Left ventricular end-diastolic pressure was elevated in two.

These studies confirm the presence of ballooning of the mitral valve in the presence of the characteristic late systolic murmur but belie the benignity of the lesion since three of seven patients had significant mitral regurgitation and another (not catheterized) had proven subacute bacterial endocarditis. The presence of the murmur at an early age suggests a congenital origin in some patients, while the mother of one patient had an identical murmur, implying a familial pattern.

Control of the Heart Rate by Paired Electrical Stimulation of the Atria (P)

John W. Lister, Emanuel Stein, Sun H. Lau, Bernard D. Kosowsky, and Anthony N. Damato, Staten Island, New York

Right-heart catheterization was performed on seven patients (aged 43 to 65) immediately after successful cardioversion for atrial fibrillation. All patients were on digitalis and quinidine. A bipolar electrode catheter was positioned in the right atrium and connected to a paired pulse pacemaker. Cardiac output and pulmonary and brachial arterial pressures were obtained during sinus rhythm, paired atrial pacing below the sinus rate, and single atrial pacing above the sinus rate. Cardiac output was determined by the dye-dilution technique.

During paired pacing of the atria, the interval between each of the pulses of a pair was from 285 to 315 msec. At this interval between the pulses, the vulnerable period of the Ta segment was avoided. Each pair of atrial depolarizations resulted in a single ventricular depolarization. The second pulse of each pair of atrial impulses was blocked at the atrioventricular node. In this study the maximum reduction in heart rate by paired atrial pacing was from 105 to 60 beats per minute (45%), and the minimum reduction in heart rate was from 75 to 60 beats per minute (20%). No arrhythmias were encountered.

There were insignificant changes in cardiac index and mean arterial pressures as the heart rate was altered by paired or single pacing of the atria.

Paired pacing of the atria with a single ventricular response to each pair of atrial impulses is a safe method for the control of heart rate.

Heart Valve Homografts (P)

Richard R. Lower, Ronald C. Pillsbury, William W. Angell, and Jon C. Kosek, Palo Alto, California

Recent reports indicating that aortic valve homografts have been used clinically in some centers stimulated this attempt to assess the long-term fate of valve homografts. Eighty-four homologous canine valve transplants, including pulmonic, aortic, and mitral replacements, were studied up to two years after operation. In vivo studies to evaluate valve function included cineradiography, cardiac catheterization, and intra-arterial pressures. Microscopic sections of the homograft valves were studied to document alterations which occur as a result of various methods of graft storage and sterilization and to detect evidence of homograft rejection. Histological studies from five hu-

man valve homografts were compared with the canine grafts.

The findings indicate that such homografts frequently retain their normal gross morphological appearance and function adequately for prolonged periods. Microscopic studies, however, demonstrated pronounced differences between valves which were freeze-dried or sterilized with beta propriolactone and those which were transplanted fresh or refrigerated for a few hours in saline. The latter group retained their cellularity over several months of observation, while the stored valves remained virtually acellular throughout the period of observation. There was no evidence of significant replenishment of fibrocytes or endothelium from host sources to the transplanted freeze-dried valves. Despite persistence of adequate elastic tissue, late changes observed in the collagen of these valves suggests that deterioration may ultimately occur.

Some New Phonocardiographic Data in Bulging of the Mitral Valve

Stein M. Lucardie and Dirk Durrer, Amsterdam, The Netherlands

In three patients who had bulging of the mitral valve demonstrated by cineangiocardiography and a late systolic murmur, new phonocardiographic data were found. A midsystolic click in two of them occurred synchronously with an incisure in the apex beat tracing. In one case this incisure was visible in the carotid artery tracing as well. In addition, one of the patients had an early systolic ejection click and two extra sounds superimposed on small vibrations. In one case the murmur was sinusoid and showed respiratory changes. In only one of the patients was mitral incompetence demonstrated by retrograde angiocardiography of the left ventricle. In all cases administration of amyl nitrite resulted in disappearance of the systolic murmur.

Apparently, it may not be possible to differentiate this syndrome from cases with an innocent late systolic murmur. Mitral incompetence does not appear to be an essential symptom in bulging of the mitral valve.

Congenital Heart Disease with Congestive Heart Failure in the Neonatal Period Following Rubella in Utero

Joshua Lynfield, Preecha Vichitbandha, Alice C. Yao, Ramon Rodriguez-Torres, and Karl E. Karlson, New York, New York

Careful examination of 29 infants with the rubella syndrome revealed the presence of cardiovascular malformations in 13. Ten were studied by hemodynamic and angiographic techniques. Our study has led to the demonstration of the following points which have not been adequately recognized previously: (1) There was a very high incidence of congestive heart failure (12 out of 13). (2) All the 12 infants in heart failure had a patent ductus; the thirteenth did not. Seven of the 12 with patent ductus arteriosus had additional lesions. Eight infants required ductal ligation for severe heart failure; six survived, and two with additional lesions died postoperatively. (3) Heart failure occurred earlier (during the first two weeks of life) than usual (after the first month of life). A good correlation existed between the age of onset of heart failure and the birth weight. The lower the birth weight, the earlier the onset of heart failure. (4) The presence of a left-to-right shunt at the atrial level in an infant with a patent ductus arteriosus is quite common, and we have demonstrated that it may disappear following ligation of the ductus. (5) Pulmonary artery branch stenosis may be a progressive lesion. The clinical course in one infant suggests this possibility. Heart failure improved following ductal ligation but then recurred two months later. At cardiac catheterization he was found to have a pulmonary artery pressure which was somewhat higher than before with bilateral branch stenosis of the pulmonary arteries.

Complications Following Banding of the Pulmonary Artery for Treatment of Heart Failure in Infants with Ventricular Septal Defect

Joshua Lynfield, Alice C. Yao, Preecha Vichitbandha, Ramon Rodriguez-Torres, and Karl E. Karlson, New York, New York

The banding procedure has become very popular in the treatment of heart failure in infants with ventricular septal defect. Our study of seven such infants over the past seven years points up the high early and late mortality and the serious complications of this procedure, which have been inadequately recognized up to now. The principal complications result from the effects of pulmonary artery obstruction produced by banding. In addition, severe fibrosis results in marked difficulties in surgical removal of the band. Only three of our seven patients have survived, and two of the three have residual obstruction following corrective surgery. Severe fibrosis in both prevented complete removal of the band. Hemodynamic studies revealed the obstruction to be moderately severe in one and mild in the other patient. The third patient is doing well but has not yet been reoperated.

The causes of death in the four patients who succumbed were as follows: One died of the procedure 24 hours after banding. The second died

20 months after banding of an anoxic spell due to thrombosis of the pulmonary artery resulting from the effects of banding. The third developed cyanosis and anoxic spells due to obstruction from the band; death followed attempted corrective surgery 18 months after banding, and very marked fibrosis prevented adequate relief of the obstruction. The fourth patient was apparently doing well but died of undetermined cause 18 months after banding.

In our experience the vast majority of infants with heart failure due to ventricular septal defect respond to medical therapy. We would recommend, on the basis of this study, that banding should be used only as a last resort in the rare infant with intractable heart failure who has failed to respond to intensive medical therapy and is too young to undergo open-heart surgery.

Myocardial Blood Flow and Rb^{86} Clearance in the Left Atrium

Delton Lyon, David B. McDaniel, and William D. Love, Jackson, Mississippi

The volume of coronary blood flow to the left atrium was measured by applying the Fick calculation to the myocardial uptake of Rb^{86} from arterial blood. The mean rate was 8.7 ± 2.1 (SD) ml/g/10 min. This was not significantly different from the average rate of blood flow to the left ventricle in the same animals. When coronary blood flow to the left ventricle was low because of a deteriorating cardiovascular status, the left atrial wall regularly received a higher rate of perfusion per gram than did the left ventricle. The rate of clearance of Rb^{86} by the atria was closely related to the rate of coronary blood flow. The error in predicting the rate of atrial blood flow from a function representing the mean relationship of atrial blood flow and Rb^{86} clearance averaged 9.6%. There was less Rb^{86} cleared at a given rate of coronary blood flow in the atria than in the ventricles. This result may have been caused by a much lower effective rate of transcapillary Rb^{86} flux in the atria or by a greatly increased amount of functional arteriovenous shunting in their walls.

Continuous Monitoring in Acute Myocardial Infarction (P)

Robert L. MacMillan, Kenneth W. G. Brown, Gerald B. Peckham, and Otto Kahn, Toronto, Ontario, Canada

Since March 15, 1962, 465 patients with proven acute myocardial infarction have been treated in a four-bed coronary unit. The electrocardiogram has been monitored continuously using a pen recorder. Subcutaneous needle electrodes inserted over the deltoid muscle cause less artifact, need no attention, and are more acceptable to patients than surface electrodes. The mortality was 33%; 54% of deaths (84 of 155) occurred during the first 48 hours and 39% (60 of 155) between the second and fifteenth day. Ninety-eight patients were monitored at the time of death. Ventricular tachycardia and fibrillation were seen most frequently (37 patients). Sinus arrest with a lower pacemaker was next in order of frequency (25 patients). Resuscitation following cardiac arrest was defined as recovery and being able to leave hospital. There were ten such patients, and all had ventricular fibrillation. In patients with a lower pacemaker, the voltage and rate might remain unaltered for several minutes after clinical death. This discrepancy between the electrical and mechanical actions of the heart requires an alarm system sensitive to both functions. Transient arrhythmias were noted in 55 of 100 consecutive patients and were more common in those who died (24 of 29) than in survivors (31 of 71). Brief asymptomatic ventricular tachycardia occurred in 17 patients but did not affect the prognosis. External pacemakers have been found useless in the treatment of cardiac arrest.

Aortic and Coronary Atherosclerosis Induced in Primates in the Absence of Hypercholesterolemia

Manuel R. Malinow, Cesar A. Maruffo, Anne M. Perley, and Robert P. Wagner, Beaverton, Oregon

An effort was made to induce atherosclerotic changes in squirrel monkeys (*Saimiri sciurea*) by the addition of cholesterol to their diet. There were 20 animals in both the experimental and control groups. The basic diet consisted of protein 16, fat 14, and carbohydrate 69 (% of cal) plus additional vitamins and salts; cholesterol (1.3 g/100 cal) was added in the first group. Cholesterol-4-C^{14} (specific activity 550 dpm/mg) was given to these animals for the last 37 days prior to sacrifice. Diets were fed for ten months. Monthly cholesterol determinations were made on all animals.

Initial and final body weights were similar in both groups. Beginning and terminal blood cholesterol determinations were also similar: 188 ± 9 (SEM) and 179 ± 7 in the control group and 196 ± 9 and 192 ± 9 mg/100 ml in the experimental group, respectively. Aortic sudanophilia on an arbitrary but reproducible score was 1.9 ± 0.5 in the controls and 5.8 ± 1.4 in the experimental group ($P < 0.02$). Coronary sudanophilia (arbitrary score) was 0.3 ± 0.2 and 5.4 ± 0.5 in the two groups, respectively ($P < 0.01$). Liver cholesterol was slightly higher in the experimen-

tal group (339 ± 14 in controls and 472 ± 46 mg/100 g wet weight in the experimental animals; $P < 0.05$). Specific activities were 364 ± 16 and 333 ± 8 dpm/mg of cholesterol in serum and liver. The results show that in these primates a high-cholesterol, low-fat diet may induce aortic and coronary atherosclerosis with normal cholesterolemia and a minimal increase in liver cholesterol. Under these conditions 60% of the plasma-liver cholesterol pool had an exogenous origin.

Phenoxybenzamine (Dibenzyline) and Renal Blood Flow

Isidore Mandelbaum, Michael Silbert, and James Berry, Indianapolis, Indiana

The role of vasodilator agents such as phenoxybenzamine (Dibenzyline) in the treatment of hemorrhagic shock and during extracorporeal circulation is a controversial one. This is a study of the effect of phenoxybenzamine on renal blood flow.

Total cardiopulmonary bypass was carried out in seven dogs. Inflow was constant into a femoral artery (80 to 120 ml/kg/min). A large inferior vena caval catheter at the level of the renal veins diverted renal flow entirely into a calibrated burette, and renal flow was determined twice. Phenoxybenzamine, 3 to 5 mg/kg, was given intravenously. The mean systemic pressure stabilized at a value lower than that of the control, and renal flow measurements were repeated. Next, epinephrine was administered. In all instances there was a further decline in systemic pressure.

The control average mean systemic pressure was 98 mm Hg (± 19), and it declined to 79 (± 14) following phenoxybenzamine. Control average renal blood flow was 194 ml/min (12.5 ml/kg/min $\pm$ 4.8) or 11.4% of pump output. After phenoxybenzamine it decreased in six animals and was unchanged in one. It averaged 179 ml/min (11 ml/kg/min $\pm$ 4.4) or 10.4% of output. Total peripheral vascular resistance decreased 19.8% and renal resistance 11% after phenoxybenzamine. These studies indicate that renal vascular resistance declines appreciably following phenoxybenzamine, but the fall in systemic resistance is nearly twice as great. Therefore, the percentage and absolute volume of total flow distributed to the kidneys decrease after this drug.

Cystine Nutriture and Cholesteremia in Rabbits and Human Beings

George Mann, Ann Frost, and Louise Garland, Nashville, Tennessee

After 55 years of study and countless experiments, the unique sensitivity of rabbits to dietary cholesterol is unexplained. Since a deficiency of cystine-methionine impairs sterol metabolism in primates, rats, and chickens, the hypothesis that rabbits lack sufficient cystine for efficiently disposing of dietary cholesterol has been examined. Specifically, cystine supplements will lessen the hypercholesteremia produced in rabbits by feeding cholesterol. When rabbits were used as self-controls in sequential experiments, this hypothesis was supported. The amount of cholesterol fed, 200 mg/day in 1,600 mg of oil, was important in the experimental design. Cortisone acetate, 2.5 mg/day orally, increases the urinary sulfur and augments the cholesteremia produced by dietary cholesterol. This kind of cholesteremia also is diminished with supplements of cystine. These findings suggested an in vitro study of liver mitochondria designed to locate an enzymatic impairment in the conversion of cholesterol to bile acids in rabbits. A feasible and sensitive means of characterizing cystine-methionine nutriture in lower animals and human beings has been developed. The subject is given a loading dose of S^{35} cystine, and the specific activity of plasma sulfur or of urinary sulfur is measured after 24 hours. Deficient animals show a higher specific activity of the sulfur isolated from either source. This assessment of sulfur nutriture is being applied to human populations for correlation with cholesteremia and susceptibility to CHD.

Congenital Anomalies of the Coronary Sinus

Emil L. Mantini, Claude M. Grondin, C. Walton Lillehei, Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

A study was made of 58 necropsy specimens with congenital anomalies of the coronary sinus. These anomalies were classified into four anatomical types:

Type I—enlargement of the coronary sinus: This anomaly results from increased flow in the coronary sinus. It occurs without left-to-right shunt with persistence of the left superior vena cava or anomalous subdiaphragmatic venous drainage into the coronary sinus. When left-to-right shunts occur, they may be low pressure, as in total and partial anomalous pulmonary venous drainage into the coronary sinus or left atrial-coronary sinus communications. High pressure shunts occur with coronary artery-coronary sinus fistulae.

Type II—absence of the coronary sinus: This anomaly occurs only in the presence of an atrial septal defect. The latter may be localized to the position normally occupied by the coronary sinus, in which case a persistent left superior vena cava is present. The defect may involve the entire lower portion of the atrial septum, as seen in persistent common atrioventricular canal and

congenital heart disease associated with asplenia.

Type III—absence of right atrial coronary sinus ostium: This condition obtains with anomalous coronary sinus drainage by three possible routes: retrograde flow in a persistent left superior vena cava, gross communication between the coronary sinus and left atrium, or via multiple communications between the coronary sinus and related atria.

Type IV—hypoplasia of the coronary sinus: This condition occurs with partial coronary venous drainage into the related atria.

Hemodynamic Effects of Ouabain in Experimental Acute Myocardial Infarction with Shock

Anthony J. Marano, Jr., Howard J. Kline, Jorge Cestero, and Leslie A. Kuhn, New York, New York

The hemodynamic effects of ouabain were investigated in dogs with acute myocardial infarction and shock produced by plastic sphere coronary embolization. Following coronary embolization there were substantial reductions of cardiac output (CO) (71%), central aortic pressure (AP) (41%), and the first derivative of the left ventricular pressure pulse (dp/dt) (63%). There was little associated rise in left atrial or left ventricular end-diastolic pressures. Ouabain (0.04 mg/kg), administered intravenously 30 minutes after embolization, produced significant elevations of CO, AP, and dp/dt in 10 of 11 animals. Average CO rose 56%, AP 40%, and dp/dt 76%, these effects diminishing one hour after injection. Systemic vascular resistance and left atrial pressure were not significantly altered. Control animals, embolized with a similar dose of microspheres and studied for a similar period, demonstrated no significant rise in CO, AP, or dp/dt in the postembolic period. In normal anesthetized animals ouabain did not produce a rise in CO or AP.

It is concluded that rapid digitalization may be of definite, although transitory, benefit in improving cardiac output and aortic pressure in acute myocardial infarction with shock, even in the absence of hemodynamic evidence of congestive heart failure.

Administration of Tritiated Digoxin Without a Loading Dose: A Metabolic Study (P)

Frank I. Marcus, Linda Burkhalter, Carol Cuccia, and Geeta G. Kapadia, Washington, District of Columbia

A single dose of digoxin is excreted in decreasing amounts each day and not as a fixed quantity daily. This observation suggests that accumulation of digoxin should occur if daily doses are given without a loading dose. An equilibrium state of tissue digoxin should be reached when excretion of digoxin rises to equal the intake of the drug. This hypothesis was tested in man and animals.

Three normal subjects were given 2.0 mg of tritiated digoxin orally on the first day, followed by 0.5 mg daily for 13 days. Three subjects received 0.5 mg daily for 14 days without an initial loading dose. Serial blood samples and collections of total urine and stool for 21 days were analyzed for activity. Comparable levels of activity in blood were found on the second day in both groups. Thereafter, the activity in blood did not increase. The subjects given the loading dose excreted much more digoxin in urine and stool for the first few days. Urinary activity was similar by the third to fifth day and remained constant during drug administration.

A study of similar design was performed in five dogs. The animals were sacrificed after one week. In two dogs given a loading dose, the myocardial concentrations were 0.020 and 0.021 μc/g (dry tissue weight), as compared with values of 0.019, 0.020, and 0.018 μc/g in the dogs not given the loading dose.

The data support the hypothesis that accumulation of digoxin does occur with daily doses without an initial loading dose. The findings suggest that a "digitalized state" can be accomplished rapidly in this manner.

Comparison of Biplane Cinecardiography and Electromagnetic Flowmeter in Measurement of Stroke Volume in Dogs

Arthur M. Martin, Jr., M. Paul Capp, Donald B. Hackel, Madison S. Spach, and Jack C. Chang, Durham, North Carolina

Stroke volumes (SV) and resultant cardiac outputs (CO) were measured in mongrel dogs weighing 15 to 25 kg before and after the induction of hemorrhagic shock (HS) at a mean arterial pressure of 35 mm Hg. Biplane cineangiocardiography (BC) and electromagnetic flowmeter (EM) measurements were made simultaneously to evaluate the correlation of the two methods. For BC the left ventricle (LV) was catheterized via the aorta, and diatrizoate was injected directly into the LV. In addition, the influence of large volume (20 ml control, 10 ml shock) and small volume (10 ml control, 5 ml shock) diatrizoate injections on the SV measurements was evaluated in all dogs. Mean CO in control animals was $1,803 \pm 664$ ml/min and during shock was 772 ± 357 ml/min. The correlation coefficient between the BC and EM for the total group was 0.79. When low volume injections were evaluated separately, the methods correlated more closely ($r = 0.88$). Evaluation of preinjection with postinjection beats by EM revealed no significant

difference in SV in low volume injection beats, but a highly significant increase in SV (and therefore CO) occurred after large volume injections ($P < 0.001$), with changes in CO of 55% in shock (777 to 1,207 ml/min) and 21% in controls (1,925 to 2,330 ml/min).

The data demonstrate that the two available methods for measuring SV have a high statistical correlation. However, highly significant errors can be induced in these measurements by injecting excessively large volumes of contrast material.

Hemodynamic Effects of Atrial Fibrillation in the Intact Dog

Richard H. Martin, Robert L. Van Citters, and Samuel T. Lim, Seattle, Washington

Previous studies have demonstrated a consistent reduction in cardiac output (CO) induced by atrial fibrillation (AF) in experimental animals. The present investigation was undertaken to determine whether a similar effect occurs in healthy, unanesthetized dogs. Six dogs were studied 10 to 20 days after the implantation of pulsed ultrasonic flow transducers, sonocardiometer crystals, and right atrial (RA) stimulating electrodes. AF with ventricular rates from 89 to 152 beats/min was induced by 50 cycle/sec stimulation of the RA. Aortic flow and pressure and left ventricular (LV) diameter were measured during sinus rhythm, AF, and atrial pacing (AP) at a rate closely comparable to the ventricular rate present during the immediately preceding AF. Resting CO, aortic pressure, and LV diameter during AF were not significantly different from those during AP in each of 13 comparisons. During treadmill exercise which doubled the resting CO during sinus rhythm, AF reduced CO by 9% and 10% in two dogs. Propranolol, 0.5 mg/kg, had no effect on CO during sinus rhythm and AP, but after this drug CO during AF was $14\% \pm 4\%$ less than that during AP in nine comparisons ($P < 0.01$). These data suggest that inotropic mechanisms may offset the loss of atrial systole during AF in the intact dog and that these mechanisms are impaired by beta adrenergic blockade.

Effects of Chlorophenoxyisobutyrate on Serum Lipids

Jack M. Martt and Gerald B. Lee, Columbia, Missouri

Thirty-three subjects with idiopathic hypercholesterolemia and coronary atherosclerosis were given ethyl chlorophenoxyisobutyrate (CPIB ester), 1 to 2 g daily, for periods up to ten months. Serum cholesterol was reduced in all but one. Prior to treatment the average serum cholesterol was 295 mg% and at the point of maximum reduction 232 mg%, a difference of 63 mg% (20%). Serum triglycerides in 12 patients before therapy averaged 177 mg% and at the termination of the study 114 mg%. Maximum response occurred after 11 weeks of treatment. A rebound of serum cholesterol to pretreatment levels was seen in all of the subjects during periods of placebo administration. Serum glutamic oxalacetic transaminase determinations revealed a transient slight rise in half of patients so tested. The only observed side effect to medication was an increase in appetite which could not be related to any demonstrable changes in the blood glucose level. The glucose tolerance test was similarly unaltered while the patients were taking medication as compared with periods of placebo administration. Desmosterol was not demonstrated in the sera of ten subjects selected at random during the treatment period.

Aortic and Coronary Atherosclerosis in Free-Ranging Howler Monkeys (*Alouatta caraya*) (P)

Cesar A. Maruffo and Manuel R. Malinow, Beaverton, Oregon

A field trip to study howler monkeys (*Alouatta caraya*) was conducted in northern Argentina. A total of 314 free-ranging animals were examined postmortem; 292 animals were found suitable for this report.

The presence of atherosclerosis (sudanophilia and/or fibrosis) in the great vessels was common. In sexually mature animals intimal lesions were observed in 90% of 131 males and in 75% of 99 females. The earliest changes were observed in the thoracic aorta and were next present in the arch and the abdominal aorta. Involvement in the iliac arteries paralleled this last one. No differences were found between male and female animals prepuberally. After puberty males had a higher involvement than females, but these differences were not significant in the oldest category. Progression of the intimal sudanophilia with age was observed in nonpregnant females, but it was absent in pregnant animals. This observation seems to suggest regression of the lesions during gestation. Only initial coronary lesions were observed; they had a similar distribution in both sexes.

Because of the apparent absence of infectious diseases, the high incidence of gross intimal changes, and the possibly sex-related arterial lesions, the howler monkey seems to be a suitable animal for experimental studies on atherosclerosis.

Maintenance of Central Blood Pressure and Total Peripheral Resistance During Competitive Thermal and Exercise Stresses

Herbert J. Marx, Loring B. Rowell, Robert D. Conn, and Robert A. Bruce, Seattle, Washington

Experiments were performed to determine whether failure to maintain central blood pressure (BP) and total peripheral resistance (TPR) during graded treadmill exercise in the presence of thermal stress is the cause of reduced physical work capacity in the heat. In six normal, non-heat-acclimatized young men, proximal aortic BP was recorded with a specially designed system immediately before and after each of seven indicator-dilution cardiac output determinations at each of four work levels (0 45 to 0.86 of maximum oxygen consumption) at 78 and 110 F. Pulse pressure did not change with increased work intensity. In five subjects at 78 F and four at 110 F, systolic pressure decreased slightly from first to second work level and increased slightly at 110 F during the fourth exercise in four men. Average systolic and pulse pressures were the same at both temperatures. TPR decreased progressively with increasing work intensity. Although at 110 F mean TPR was slightly lower during the first two workloads than at 78 F, it was slightly higher thereafter. At 110 F central blood pressure and TPR were maintained well despite further enlargement of the peripheral vascular compartment by adding thermally induced cutaneous vasodilatation to muscular vasodilatation. Greater visceral vasoconstriction during exercise at 110 F than at 78 F, shown in previous studies, apparently provides an effective means of maintaining perfusion pressure. Excessive heart rates were maintained in association with undiminished mean pressure. Diminished work capacity in the heat is not due to hypotension or reduced TPR but is more likely related to cardiac performance.

Time to Peak dp/dt: A Useful Measurement for Evaluating the Contractile State of the Human Heart

Dean T. Mason, Edmund H. Sonnenblick, John Ross, Jr., James W. Covell, and Eugene Braunwald, Bethesda, Maryland

The maximum rate of intraventricular pressure rise (dp/dt) has been used extensively in assessing the myocardial contractile state; however, alterations in ventricular preload and afterload can also affect this variable. In 12 isolated human papillary muscles contracting isometrically, the contractile state was always an inverse function of the time interval from the onset of contraction to the maximum dp/dt (t − dp/dt). In ten experiments in a canine heart preparation in which preload, afterload, and contractile state could be varied independently, t − dp/dt was also inversely related to the contractile state, regardless of loading conditions. Although t − dp/dt could be abbreviated by premature opening of the semilunar valves, a decrease in dp/dt accompanied this event. It thus appeared that an elevation of dp/dt in the face of a decline in t − dp/dt always reflects an augmentation of the heart's contractile state, and studies were undertaken to utilize these concepts in man. High fidelity left ventricular pressure and dp/dt were recorded in conscious patients, and t − dp/dt was measured. Isoproterenol (six patients) raised dp/dt from 1,535 to 2,580 mm Hg/sec, while t − dp/dt shortened from 80 to 57 msec. Exercise (six patients) and ouabain (four patients) had similar effects. Interventions known not to influence contractile state, such as sudden elevation of preload by leg raising (five patients) and increasing afterload with methoxamine (eight patients), did not influence t − dp/dt, despite elevating dp/dt. In conclusion, the combination of t − dp/dt and dp/dt provides a useful, simple, and experimentally validated approach to assessing the contractile state of the heart in intact man.

Cineangiographic Appraisal of Mitral Valve Function During Atrial Fibrillation and Premature Ventricular Contractions

Nosrat A. Massih, Paul H. McDermott, Vincent Runco, Hugh S. Levin, and Richard W. Booth, Omaha, Nebraska

Since criteria for semiquantitative estimation of mitral regurgitation during left ventriculography depend on systolic regurgitation of dye, it is essential to know whether arrhythmias in general and atrial fibrillation in particular produce incompetency of normal valves or enhance regurgitation through damaged ones. Experiments designed to gain this information have yielded conflicting results regarding both the existence of regurgitation during arrhythmias and the phase of the cardiac cycle in which it occurs.

To assess the problem further, normal anesthetized dogs, weighing 15 to 30 kg, were subjected to retrograde left ventricular catheterization. Special attention to catheter placement avoided false regurgitation from artifactual distortion of the valve. Constant infusion of acetylcholine allowed atrial fibrillation and sinus rhythm to be produced at will by external electroversion. In each animal repeated left ventricular cineangiograms were performed alternately during sinus rhythm and atrial fibrillation with identical amounts of contrast media and injection pressures. The position of the cathe-

ter tip was rechecked each time. A total of 100 satisfactory injections were accomplished.

Mitral regurgitation did not occur during sinus rhythm. In almost every case, however, atrial fibrillation was associated with significant degrees of regurgitation during systole and diastole. Premature ventricular contractions caused diastolic regurgitation during long compensatory pauses, and with the next normal beat the unexpected finding of systolic regurgitation was frequently observed.

It is concluded that at least in dogs, atrial fibrillation and premature ventricular contractions cause incompetency of normal mitral valves and that the regurgitation occurs in systole as well as diastole.

Studies on the Mechanism of Cardiac Arrhythmias in Cheyne-Stokes Respiration

Rashid A. Massumi and Donald O. Nutter, Washington, District of Columbia

Phasic cardiac slowing (sinus bradycardia to complete atrioventricular block) related to Cheyne-Stokes respiration (CSR) has been known for almost a century, but its mechanism has not been investigated. This report is concerned with a battery of pressure and gas studies in arterial and internal jugular blood and in cerebrospinal fluid (CSF) during various phases of CSR in 12 patients, six of whom had CSR-related cardiac arrhythmias. The purpose was to determine the magnitude of cyclical fluctuations in these parameters and to correlate them with cardiac rate and rhythm.

Cardiac slowing or atrioventricular block, sometimes associated with a marked fall in blood pressure, occurred in late apnea or early hyperpnea, while sinus tachycardia was present during late hyperpnea and early apnea. The invariable disappearance of arrhythmia and blood pressure fluctuations after intravenous atropine proved mediation of the vagus, usually stimulated by digitalis. Frequent sequential sampling of blood showed paradoxically low arterial PCO_2 and high PO_2 in mid-apnea and a swing to the opposite extreme in hyperpnea. In CSF pressure rose markedly at the time of cardiac slowing, and gas tensions and pH fluctuated considerably. The investigation showed that the cyclical variations in vagal tone leading to profound disturbances of cardiac rhythm are brought about by the combined influences of a rise in CSF pressure, a rise in arterial PCO_2, and probably a fall in arterial PO_2. The possible role of CSF gas tension and pH fluctuations in the genesis of arrhythmia is discussed in the report.

Superior Vena Cava to Right Pulmonary Artery Versus Blalock Shunts: Comparison of the Effects of Respiration, Exercise, and Drugs on Blood Flow Through the Shunts

Ichiro Matano, Edward P. Call, and William W. L. Glenn, New Haven, Connecticut

The superior vena cava to right pulmonary artery anastomosis (SVC-RPA) and systemic artery to right pulmonary artery anastomosis (Blalock shunt) were compared in anesthetized and unanesthetized dogs. Electromagnetic flowmeter studies were performed immediately postoperatively and again five to 21 days later.

The effects of respiration on flow were examined in normal and positive pressure respiratory cycles and after radiofrequency phrenic nerve stimulation. Passive and active exercise was evaluated, as well as vasodilating agents, histamine, and catecholamines.

In normal respiration and after phrenic nerve stimulation, the inspiratory phase was accompanied by an increase of 10% and 15%, respectively, in SVC-RPA flow. Positive pressure reduced the flow during this phase by 50% and also reduced the mean flow by 25%. By contrast, little change was seen in flow through the Blalock shunt in these studies.

Passive exercise under light pentobarbital sodium anesthesia increased SVC-RPA flow by 40%, and active exercise on a treadmill while awake increased flow by 125%. Concomitantly, SVC pressure was doubled in each case. By contrast, flow through the Blalock shunt in these two experiments was only moderately increased with no change in central venous pressure.

In SVC-RPA dogs, when drugs were injected through the inferior vena cava, systemic effects were immediately observed. If injected through the superior vena cava, the action of these drugs on the pulmonic circulation could be evaluated before systemic and cardiac effects occurred. These pulmonic effects were not seen in dogs with Blalock shunts.

Electromechanical Correlations in Subaortic Stenosis (P)

Virendra S. Mathur, Michael D. Klein, Harold D. Levine, and Richard Gorlin, Boston, Massachusetts

Electrocardiographic and vectorcardiographic findings in 14 cases of muscular subaortic stenosis (SAS) were analyzed and correlated with hemodynamic and cineangiographic results obtained at catheterization. The maximum spatial vector (MSV), calculated by the Pythagorean theorem ($MSV = \sqrt{x^2 + y^2 + z^2}$), was found to average 6.5

mv with individual values ranging between 3.15 and 15.10 mv. When peak left ventricular pressure, augmented during isoproterenol stress, was plotted against the MSV, electrical voltages were disproportionately high in contrast to cases of valvular aortic stenosis. These remarkably high voltages emphasized that ventricular hypertrophy in SAS probably emanates from a primary disorder of muscle growth rather than as a consequence of increased left ventricular pressure secondary to outflow tract obstruction. From a pattern point of view, nine of the 14 subjects showed abnormal Q waves resembling myocardial infarction on the electrocardiogram. Vectorcardiography revealed normal spatial vectors during the first 10 msec in 11 of 14 cases, in contradistinction to patients with myocardial infarction where early deviations from the normal conduction pattern are often evident. Abnormalities in 20- to 40-msec instantaneous vectors fell into three groups: in three cases these forces were directed anterosuperiorly; in four cases posteriorly; in two cases rightward and anteroinferiorly. The specific pattern of conduction abnormality may discriminate between the location of abnormal septal hypertrophy and whether it is localized or diffuse. The extent and location of septal hypertrophy will have important implications in determining the type of surgery to be attempted for correction of muscular SAS.

Circulatory Effects of Sympathetic Blockade and Ganglionic Blockade in Unanesthetized Dogs

Robert A. Maxwell, Burlington, Vermont

This study was undertaken to determine normal values for mean aortic pressure (MAP), stroke volume (SV), heart rate (HR), total peripheral resistance (TPR), and cardiac output minus coronary flow (CO) in quiet, standing, unanesthetized dogs and to study the influence of drug-induced sympathetic blockade and ganglionic blockade on these parameters. Electromagnetic flowmeter probes were implanted around the ascending aortae of 20 dogs, and tygon catheters were passed through the subclavian arteries into the aortae distal to the probes. The flow signal for each beat was integrated electronically to yield SV, and the integrals were summed for ten-second intervals to give CO. Heart rate was recorded with a Grass tachograph. The magnitude of the reflex circulatory changes elicited by occlusion of the common carotid arteries, which had been explanted previously into tubes of skin, was used as an index of sympathetic activity.

Cardiac output was a reasonable constant variable when sampled frequently over a four-week period, although SV and HR varied reciprocally over a wide range. TPR fluctuated so as to yield MAP from 75 to 120 mm Hg. Large doses of sympathetic blocking agents did not consistently alter CO but uniformly lowered TPR to the "floor" value observed during the control studies in each animal. As a consequence, MAP was usually lowered to 75 mm Hg. Large doses of ganglionic blocking agents reduced TPR to "floor" value and often reduced CO with a consequent reduction in MAP below 75 mm Hg.

It is concluded that drug-induced sympathetic blockage has only negligible effect on CO and modest effect on TPR in quiet, standing, unanesthetized dogs. A considerable component of TPR appears to be sustained by an extrasympathetic mechanism.

Effects of Physical Training on Exertional Myocardial Ischemia in Middle-aged Men

John A. Mazzarella and John W. Jordan, Jr., Seattle, Washington

Inasmuch as physical conditioning following convalescence from acute myocardial infarction may diminish exertional myocardial ischemic responses, the possibility of reversing this ischemic response prior to infarction was investigated. After clinically screening 100 male university personnel, seven men ranging in age from 41 to 69 years were selected; six were asymptomatic, one had angina, and all were normotensive with normal 12-lead resting electrocardiograms. Electrocardiographic responses to multistage maximal exercise testing showed four subjects with from 1- to 3-mm depression of ST, one subject with borderline response, and two subjects with normal tracings. Measured maximal oxygen consumption ranged from 23.2 to 41.4 ml/kg/min; maximal heart rates ranged from 150 to 198.

Physical training consisted of 20 minutes' treadmill walk thrice weekly for eight to ten weeks with a constant work load for each subject calculated to approximate 73% (range 64 to 86%) of his maximal oxygen consumption. Magnetically recorded electrocardiographic responses to multistage testing before and after physical training were quantitated by computer analysis. At the conclusion of training, three men showed reduction of less than seven beats in maximum heart rate ($P < 0.05$), and six men demonstrated increased exercise capacity. Four men showed increased maximal oxygen consumption (range 2.3 to 8.6 ml/kg/min). Six men showed less ST depression to submaximal work after training, five showed improvement at maximal exercise, while only three exhibited ST depression in their immediate postexercise electrocardiogram.

Supervised physical training for increasing work capacity and diminishing exertional myocardial

ischemia is practical, safe, and sometimes beneficial.

Sequential Myocardial Changes Following Induced Pulmonic Stenosis

Davis C. McCool, William C. Woolverton, and Keith Reemtsma, New Orleans, Louisiana

The purpose of this study was to evaluate sequential changes in myocardial hypertrophy and coronary arterial volume following induced pulmonic stenosis in dogs. Of 36 animals subjected to narrowing of the main pulmonary artery, 22 succumbed within one month. Ten animals were evaluated at one month and four at four months with cardiac catheterization, estimations of right and left coronary arterial volume by barium-latex injection under physiological pressures, and measurement of right and left ventricular weights. (The septum was included with the left ventricle because the left coronary artery in the dog supplies the entire septum; the right coronary supplies only the lateral wall of the right ventricle.) An additional 40 hearts were used as controls.

Results showed hypertrophy of both right and left ventricular masses, with a greater increase in the right one month after operation, but there was no significant further increase in specimens studied four months postoperatively. The RV/LV weight ratio was 26% in controls, 38% at one month, and 42% at four months. Volumetric injection studies showed a preponderant increase in volume of the right coronary artery (RCA), and the RCA volume/RV weight ratio was greater at one month than at four months postoperatively.

These studies suggest that acute pulmonic stenosis in dogs is followed by sequential changes, consisting of early expansion of coronary vasculature relative to the development of myocardial hypertrophy.

Effect of Induced Hyperlipemia on Angina Pectoris

Brian G. McDade, Tarrytown, New York, Ali Navab, and John S. LaDue, New York, New York

Forty patients with angina pectoris but with normal or only slightly abnormal resting electrocardiograms were subjected to the effects of nonfat and 0.4 g/kg of saturated fat feedings on successive days. Monitored exercise electrocardiograms were done one and four hours after the feedings. Control, one-hour, and four-hour estimations were made of the serum lipids, including cholesterol, cholesterol esters, total lipids, phospholipids, esterified fatty acids, beta-lipoproteins, and Sf 0-12 and Sf 12-400 lipoproteins, and of streptokinase dose prediction tests, plasma euglobulin, whole blood clotting time by a thromboelastograph, serum turbidity, routine complete blood counts, hematocrit, sedimentation rate, glucose, urea, and SGO-transaminase.

The patients readily separated into two groups: group I with negative and group II with positive monitored control ECG exercise tests. The patients with positive exercise tests demonstrated a greater increase in serum turbidity, total lipids, fractionated lipids, and triglycerides after fat feedings. The decrease in fibrinolytic activity was also significantly greater in group II. This observation suggests that abnormalities in the handling of saturated fat loads may be an index of susceptibility to myocardial ischemia.

Phlegmasia Cerulea Dolens: Early Recognition and Management (P)

Joseph F. X. McGarvey, Edward W. Ehrlich, and Daniel Mason, Philadelphia, Pennsylvania

A discussion of the pathophysiology of phlegmasia cerulea dolens in man and animals is followed by the presentation of the management of five cases that were diagnosed with this condition. The surgical technique, the findings at surgery, and the value of postoperative heparinization are included in the report. The association of carcinoma and previous surgery led a list of seven other conditions which preceded the development of phlegmasia cerulea dolens in 42 of 149 cases in the literature. In 81 of 155 cases (52%) which were managed medically, gangrene developed. The death rate in this same collected series was 42 of 155 cases (27.7%). Medical management led to venous sequelae in 24 of 155 cases (15.5%).

Three of our five cases were successfully managed by early thrombectomy with no postoperative sequelae. In the other two cases diagnosis of phelgmasia cerulea dolens was made after a pulmonary emboli in one and after symptoms were present for six days in the other. Both patients came to surgery late in the course of their disease and died.

Thus, our review stresses the importance of early diagnosis and early surgical intervention in an effort to reduce the mortality and morbidity often associated with this disease.

Role of Acetylcholine in the Renal Vasoconstrictor Response to Sympathetic Nerve Stimulation (P)

John C. McGiff,† Robert B. P. Burns, Philadelphia, Pennsylvania, and Marvin R. Blumenthal, New York, New York

It has been proposed by Burn and Rand that acetylcholine (ACh) liberates the sympathetic

neurotransmitter following sympathetic nerve stimulation. In the present study the renal blood vessels were examined for a cholinergic determinant of their response to renal nerve stimulation. In dogs anesthetized with chloralose, mean aortic pressures and renal blood flows (RBF) were measured continuously by rotameter or electromagnetic flowmeter. All drugs were administered in the renal artery in order to reduce extrarenal effects. Control values were blood pressure 147 ± 4 mm Hg and RBF 257 ± 12 ml/min. ACh in doses of 1, 10, and 100 μg increased RBF by 10 ± 2%, 13 ± 3%, and 7 ± 3%, respectively, whereas 1,000 μg of ACh reduced RBF by 35 ± 8%. After atropine and physostigmine 1 μg of ACh did not alter RBF, while 10, 100, and 1,000 μg of ACh reduced RBF by 6 ± 3%, 40 ± 6%, and 72 ± 4%, respectively. The vasoconstrictor action of ACh was due to liberation of norepinephrine, for phentolamine opposed it. Guanethidine and hexamethonium also blocked the vasoconstrictor effect of ACh. However, hexamethonium did not block the renal vascular response to renal nerve stimulation, whereas guanethidine did. The differential effects of hexamethonium on the renal vascular response to nerve stimulation and ACh suggest that it opposes the effect of ACh by barring its entry at the membrane of the nerve terminals, whereas guanethidine opposes the release of norepinephrine by ACh within the nerve ending. The vasoconstrictor response to renal nerve stimulation was reduced by atropine and augmented by physostigmine. Hemicholinium, which depletes ACh from nerve endings, opposed the renal vasoconstriction elicited by renal nerve stimulation only if the frequency of nerve stimulation was above a critical level (usually 7 pulses per second). The data suggest that ACh may function in the canine kidney to liberate norepinephrine during activity of the sympathetic nerves.

Effects of Intra-Arterial Acetyl Strophanthidin on the Lower Extremity of Man (P)

Henry D. McIntosh, James Rouse, Carl J. Gerber, Ralph E. Thiers, and James J. Morris, Jr., Durham, North Carolina

The present study demonstrates for the first time the local effect of acetyl strophanthidin (AS) on potassium (K) release and the circulation within an area of skeletal muscle in man. Previous studies have shown a loss of K from isolated heart, liver, and skeletal muscle, as well as K release from intact coronary and portal circulations.

Bilateral femoral arterial and venous samples in 12 normal subjects were analyzed for serum K before and 1, 4, 7, 10, 20, and 30 minutes after unilateral arterial infusion of 1.0 mg AS. The contralateral leg served as the control. AS produced an immediate, small, but significant rise ($P > 0.05$) of K in the venous blood leaving the "digitalized" extremity. This localized hyperkalemia persisted for ten minutes, after which the arterial level rose slightly. No significant changes in pH, pO_2, sodium, or glucose were observed. Paresthesias promptly developed (one to two minutes) in the leg receiving the AS and were followed by deep muscle cramps and fasciculations (ten plus minutes). Xenon washout studies showed either a coincident decrease or minor changes in muscle blood flow. No effect was observed on heart rate or left ventricular ejection time (LVET). On the other hand, the same dose of AS injected intravenously one week later resulted in an immediate and significant decrease in heart rate with no change in the duration of LVET.

This study demonstrates that intra-arterially infused AS is promptly removed by skeletal muscle in man and produces predominantly local effects which include K release and decreased blood flow. Such infusions of AS do not lead to the cardiovascular changes produced by intravenous administration of similar doses.

Thrombotic Vascular Disease in Homocystinuria, a Newly Recognized Inborn Error of Metabolism Simulating Marfan's Syndrome (P)

Victor A. McKusick, R. Neil Schimke, Thomas Huang, and Abou D. Pollack, Baltimore, Maryland

Fourteen families with 26 affected persons were identified, mainly by screening the urine of patients with nontraumatic ectopia lentis and/or presumed Marfan's syndrome. The ages of living affected persons ranged from six to 45 years. Six died at ages ranging from three to 28 years. Autopsy material from three was studied. Inheritance was autosomal recessive; Marfan's syndrome is dominant.

Clinical features simulating Marfan's syndrome were (1) ectopia lentis, myopia, and retinal detachment and (2) skeletal abnormalities, e.g., long extremities, scoliosis, and pectus excavatum. Features unknown in Marfan's syndrome were (1) osteoporosis, (2) mental retardation (in 16), and (3) thrombotic vascular disease. Drastic histological changes in the media of coronary, carotid, renal, femoral, and subclavian arteries led to dilatation and thrombosis. Thrombosis of the abdominal aorta, recurrent thrombophlebitis, pulmonary embolism, and fatal thrombosis of the portal vein were observed.

Clinical manifestations of the arterial changes included coronary occlusion (e.g., fatal in a 20-year-old female), hypertension, arterial bruits, absent pulses, claudication, and localizing neurological signs. No aortic diastolic murmur was

found. Two patients had an inconstant apical mid-diastolic murmur; a mitral opening snap was present in one of these, with extensive left atrial endocardial fibroelastosis found at autopsy. Facial flushing and livedo reticularis were frequent.

Hepatic cystathionine synthetase was assayed in three of the 26 patients and found virtually absent. No abnormality of platelet adhesiveness, platelet survival, or coagulation parameters was demonstrated. Cystathionine synthetase is normally absent from platelets.

Demonstration of Ventricular Aneurysms by Radioisotope Scanning

David C. Meek, Donald W. Brown, Carlton L. Schmock, and S. Gilbert Blount, Jr., Denver, Colorado

Successful surgical resection of ventricular aneurysms has focused interest on this entity. This study was undertaken to determine the value of radioisotope scanning in ventricular aneurysms.

Fourteen patients with ventricular aneurysms were accepted for the study on the basis of typical electrocardiographic and roentgenographic or fluoroscopic findings. Rectilinear scanning after the administration of 300 μc of I^{131}-labeled iodipamide was performed.

Five of the 14 patients demonstrated a bulge on an anterior-posterior roentgenogram, and the scan showed radioactivity in the area of the bulge. This observation was interpreted as showing filling of the aneurysm and therefore implied that little if any mural thrombus was present. One patient expired, and autopsy confirmed the absence of a thrombus, as initially suggested by the scan.

Five of the 14 patients showed nonfilling of the bulge area, and this was thought to demonstrate the presence of a significant mural thrombus.

Four of the 14 patients did not demonstrate a bulge on the anterior-posterior roentgenogram silhouette, and the scans correlated with the X-ray in being either normal or showing cardiac dilatation.

These results suggest that scanning is a useful technique in assessing the presence or absence of mural thrombi in ventricular aneurysms.

Enterovirus Infection and Endocardial Fibroelastosis (P)

Ali Mehrizi, Grover M. Hutchins, Donald N. Medearis, Jr., and Richard D. Rowe, Baltimore, Maryland

Results of retrospective studies have suggested that Coxsackie Group B viruses may be etiological factors in the production of endocardial fibroelastosis, but prospective observations have not been described. Two children whose initial cardiac illness was temporally associated with an enterovirus infection and whose postmortem examination revealed endocardial fibroelastosis were recently observed at the Johns Hopkins Hospital. During early infancy both children were well. At seven and 11 months of age they developed respiratory disease and signs of myocarditis and cardiac failure. From the stool of the first child, poliovirus type II was recovered, and an eightfold rise in titer of homotypical neutralizing antibody was detected. From the stool of the second, Coxsackie B5 virus was isolated. An acute serum was not obtained, but the titers of homotypical neutralizing antibody three and seven months later were 1:320 and 1:160. The subsequent course of both of these children was prolonged cardiac failure with remissions and exacerbations. At autopsy, at the ages of 37 and 22 months, respectively, both were found to have endocardial fibroelastosis. Neither heart yielded virus on inoculation of monkey kidney or Hela cell cultures (other attempts to recover virus are being made). These observations are consistent with the hypothesis that some cases of endocardial fibroelastosis are sequelae of an enterovirus-induced myocarditis.

Correlation of Electrocardiographic Findings with Cardiodynamic Data in Valvular Stenosis

Julius G. Mendel and George E. Seiden, New York, New York

Electrocardiograms of patients with mitral and aortic stenosis who had right- and left-heart catheterizations were correlated with the hemodynamic data. Patients were selected who had adequate flow and gradient studies and who had qualitative evaluation of aortic insufficiency by angiograms or semiquantitative evaluation of mitral regurgitation by dye techniques.

Of 32 patients with mitral stenosis, 12 had electrocardiographic evidence of right ventricular hypertrophy or mean electrical axis of +90° or greater. Valve areas in this group ranged between 0.3 and 1.6 cm^2. Twenty patients without these electrocardiographic findings had valve areas between 0.5 and 1.5 cm^2. The presence of right ventricular hypertrophy correlated well with the higher right ventricular systolic pressures ($P > 0.01$), but no correlation was found between this electrocardiographic finding and the valve area, mitral pressure gradient, or right ventricular end-diastolic pressure.

Of 17 patients with aortic stenosis, ten had definite electrocardiographic evidence of left ventricular hypertrophy. Aortic valve areas in this group ranged between 0.3 and 0.9 cm^2. Seven patients with absent or equivocal evidence of left ventricular hypertrophy had valve areas between

0.4 and 1.0 cm^2. Significant elevation of left ventricular end-diastolic pressure ($P > 0.01$) and of the aortic gradient ($P > 0.01$) was found in the hypertrophy group.

In mitral and aortic stenosis the finding of a normal or nonspecific electrocardiogram does not preclude tight stenosis. In aortic stenosis, in the absence of hypertension, the finding of left ventricular hypertrophy correlates well with higher gradients and higher left ventricular end-diastolic pressures.

Hypergranularity of the Preglomerular Arteriolar Smooth Muscle in Microembolic Renal Ischemic Hypertension in Rabbits (P)

William A. Mersereau and Sean Moore, Montreal, Quebec, Canada

The observation of a close relationship between complicated aortic atherosclerosis above or at the origins of the renal arteries and the presence of small atrophic scars of the surface renal cortex led to a study of embolization of the kidneys using platelet masses. Hypertension was produced by means of an embolic source composed of MgAl wire (98% Mg), covered, except for small areas, by plastic (vinyl or celloidin), and placed in the thoracic aorta of rabbits. The present communication demonstrates that hypergranulation of the afferent arterioles and intertubular arterioles correlates with the development of hypertension and areas of tubular atrophy occurring along the renal cortical surface. Granules were demonstrated by Goldner's modification of Masson's trichrome and confirmed by fluorescence microscopy employing thioflavine T. In an experimental group of nine rabbits carried from two to five weeks, all developed hypertension, atrophic tubular lesions, marked intimal hyperplasia of intertubular arterioles proximal to the atrophic areas, and prominent hypergranulation of the vessel walls distal to the intimal thickening. Uninvolved areas showed no granularity of the juxtaglomerular arterioles, suggesting degranulation. Seven control rabbits did not develop hypertension or atrophic lesions and had normal distribution of juxtaglomerular granularity. It is concluded that the increased granularity of vessels in areas of focal ischemic atrophy due to platelet microemboli results in the initiation of hypertension, probably mediated by the renin-angiotensin system.

Cerebral Hemodynamics and Metabolism During Breath-holding and the Valsalva Maneuver (P)

John S. Meyer, Fumio Gotoh, Yasuyuki Takagi, and Ryoji Kakimi, Detroit, Michigan

Cerebral hemodynamic and metabolic changes during breath-holding and the Valsalva maneuver were compared in subjects with and without stroke. Arterial and internal jugular venous blood were continuously monitored, using new methods for oxygen tension (PaO_2, JPO_2), saturation (SaO_2, JSO_2), carbon dioxide tension ($PaCO_2$, $JPCO_2$), pH (apH, JpH), sodium (aNa^+, JNa^+), and potassium ionic activity (aK^+, JK^+). Blood pressure, expired CO_2, and the electroencephalogram were simultaneously recorded during breath-holding and the Valsalva maneuver in 16 volunteers.

During tolerated breath-holding cerebral venous PO_2 and saturation increased after an initial small fall despite decreased arterial PO_2 and saturation. $PaCO_2$ increased after an initial small decrease, but $JPCO_2$ did not change. The increase in cerebral venous oxygen was independent of arterial oxygen but depended on increased arterial PCO_2. Arterial pH decreased after slight increase, but cerebral venous pH did not change. Arterial and jugular Na^+ and K^+ showed no change.

During the Valsalva maneuver cerebral venous PO_2 and saturation decreased despite increased arterial PO_2 and saturation. Arterial CO_2 slightly decreased but showed no correlation with cerebral venous oxygen change. Arterial pH increased slightly. No changes were found in cerebral or arterial venous PCO_2, pH, Na^+, or K^+.

During tolerated breath-holding the brain does not become hypoxic in subjects with or without stroke. Oxygen becomes more available as a result of cerebral vasodilatation from elevated arterial CO_2. During the Valsalva maneuver, the brain does become hypoxic because cerebral blood flow decreases as blood pressure decreases (and venous pressure increases). Hence, with cerebral vascular disease, symptoms are likely (i.e., tussive syncope, micturition syncope, stroke).

Nonspecific Electrocardiographic Abnormalities Associated with Neurological Disease

Kay Millar and J. A. Abildskov, Syracuse, New York

Striking electrocardiographic abnormalities, consisting of large prolonged T waves, are known to occur with neurological disease. This study suggests that less striking ST-T abnormalities, simulating those in cardiac disease, may also result from neurological lesions.

Standard electrocardiograms were recorded on 47 patients with a variety of neurological lesions, including brain tumors, trauma, infection, and vascular accidents. Patients ranged in age from four months to 45 years. None had symptomatic, physical, or X-ray evidence of cardiac disease. Tracings were evaluated independently by three cardiologists without knowledge of the patients' clinical states.

Of a total of 130 electrocardiograms, 60 were normal, 43 were abnormal, and in 27 there was disagreement among the interpreters. In 38% (18 of 47) of the patients, all electrocardiograms recorded were normal. In 36% (17 of 47), at least one tracing was interpreted as abnormal by all three readers.

The most common findings were abnormalities of T-wave form and ST displacements. Some had prolonged QTC or large U waves. Three patients showed serial T-wave changes, but tracings were individually within normal limits.

The high incidence of abnormal tracings in these young people with presumably normal hearts suggests the likelihood of important and frequent diagnostic errors in the widespread practice of attributing nonspecific electrocardiographic abnormalities to cardiac disease. The study does not elucidate the mechanism of the abnormalities, but direct neurogenic effect on the heart seems most likely, perhaps by altered sympathetic tone, which is known to have profound effects on ventricular action potentials and refractory period.

Specific Beta-Glucuronidase Activity in Serum of Patients with Chronic Coronary Artery Disease

Benjamin F. Miller, Frances P. Keyes, and P. William Curreri, Philadelphia, Pennsylvania

Activity of beta-glucuronidase increases in atherosclerotic human arteries. Also, its activity in serum correlates with resistance of a species to atherosclerosis. Recently, Fishman has developed a highly specific method for assay of beta-glucuronidase which prevents interference by serum inhibitors. We have applied the specific method in patients with established, chronic coronary atherosclerosis.

In the specific method enzyme activity was determined on 0.2 ml serum at 37 C in acetate buffer, pH 4.6, with 0.006 M phenolphthalein-glucuronide substrate for four hours. In the standard, nonspecific method 0.001 M phenolphthalein-glucuronide is used with 20 hours incubation. Results are expressed in both methods as micrograms phenolphthalein released per 100 ml serum per hour.

Average specific beta-glucuronidase activity in sera of 20 patients with coronary atherosclerosis was 2,260 (range 810 to 5,310), as compared with 1,140 (range 390 to 1,930) in 20 individuals of comparable age without clinical or electrocardiographic manifestations of coronary atherosclerosis ($P < 0.001$). By the nonspecific procedure the average for coronary patients was 550 (range 250 to 910) and 480 (range 110 to 850) for the controls ($0.3 < P < 0.4$). The inhibition is equivalent to 1,710 units in the coronary group and 660 in the controls.

Average serum beta-glucuronidase activity, determined by the specific method, is elevated in chronic coronary atherosclerosis. Also, the activity of inhibitory substances increases in coronary patients.

Venous Replacement Utilizing the Adjunct of a Temporary Arteriovenous Fistula (P)

Hiroshi Mitsuoka, Rogelio E. Vega, and John M. Howard, Philadelphia, Pennsylvania

Studies over the past six years in this laboratory have indicated the failure of most prostheses and venous homografts followng their insertion as replacement of segments of the venous system in dogs. Pilot studies suggested that an arteriovenous fistula tended to permit venous homografts to remain patent.

In the current study ten dogs underwent replacement of the superior vena cava with Teflon grafts. After 16 weeks the patency rate was 60%. In the second series 12 dogs had the same operation, except that a small, 4- to 5-mm arteriovenous fistula was created craniad to the graft. After three weeks the arteriovenous fistula was surgically closed. All grafts remain patent at this time (12 weeks). In the third series the longer grafts, 7 to 10 cm, were transplanted on the superior vena cava with arteriovenous fistula. This series resulted in 80% patency rate after ten weeks. The influence of arteriovenous fistula on the heart, by recording electrocardiogram, blood pressure, and blood flow rate of the superior vena cava, was included in the study.

The results have been far superior to any previously obtained in this laboratory.

Abnormal Bohr Effect: A Possible Cause of Myocardial Ischemia (P)

Hiroshi Mizukami and Robert S. Eliot, Minneapolis, Minnesota

Among patients having chest pain suspected to be due to coronary disease, objective evidence is often lacking. Paradoxically, for example, coronary arteriograms may fail to reveal abnormality, whereas the Master two-step test is found to be positive. Three such patients and eight normal controls were studied by means of hemoglobin-oxygen absorption and the Bohr effect.

The sigmoid nature of the hemoglobin-oxygen absorption curves in the eight normals and the three abnormal patients was the same. Hill's constant "n" was 2.9 in both the normals and "abnormals." However, the oxygen affinity of the "abnormals" was found to be lower than that of the normals. For instance, 50% oxygen saturation

of normal hemoglobin was attained at 8 mm Hg partial pressure of oxygen and at a pH of 7.0 in 0.05 M phosphate buffer at 20 C, while the hemoglobin of "abnormals" was saturated to 50% at 10 mm Hg. Consequently, the Bohr effect of these patients was found to be shifted toward the basic side by about 0.3 pH units.

Such a shift in the pH of the Bohr effect may be responsible not only for the decrease of the total oxygen binding capacity of hemoglobin, but also for a decrease in the efficiency of uptake as well as the release of oxygen in vivo. This abnormal physiological response may be a possible explanation for the clinical picture of coronary artery disease when angiocardiographic evidence is found to be lacking. Studies to determine the cause of this abnormality and its possible correction are underway.

Valvular Involvement in Chorea and Rheumatic Fever (P)

Madhu R. Mody and Benedict F. Massell, Boston, Massachusetts

Adults with pure mitral stenosis not infrequently give a history of chorea as the only manifestation of rheumatic fever in childhood. It was of interest, therefore, to review the records of children with carditis and chorea to determine which valves were involved. Of 3,114 patients under the age of 17 years observed during first admissions to this hospital during 1921–1960, 68 had chorea and carditis without any other manifestations of acute rheumatic fever (ARF). Two other groups matched for year of admission, age, and sex served as controls: (1) patients with ARF and carditis and (2) patients with ARF, chorea, and carditis. Patients with more than one attack of chorea or ARF were excluded from all three groups.

Sixty-seven of the 68 patients with pure chorea had mitral valvulitis alone, as manifested by mitral systolic or diastolic murmurs. Only one had mitral and aortic involvement. Controls with ARF and carditis included 43 patients with mitral involvement alone and 25 with both mitral and aortic lesions. Controls with ARF, chorea, and carditis included 48 patients with mitral lesions alone, 17 with both mitral and aortic lesions, and three with pure aortic regurgitation.

The rarity of aortic valve involvement in the group with chorea and carditis compared to controls is significant and may explain the relatively high frequency of pure mitral stenosis in adults. Initial mitral regurgitation during chorea might lead to subsequent mitral stenosis by gradual fibrosis of the injured mitral valve.

Myocardial Ultrastructure During Systole and Diastole (P)

Robert C. Monroe, Walter J. Gamble, Clarence L. Morgan, Raul Gamboa, and Stanley Bullivant, Boston, Massachusetts

A method has been devised to obtain biopsy specimens for electron microscopy of heart muscle in both systole and diastole. Tubular stainless steel projectiles, 0.8 mm outside diameter, were accelerated to supersonic velocities by an explosive, programmed to pass through the left ventricular myocardium of an isolated, supported dog's heart in specific phases of the contraction cycle, and decelerated in partially frozen propane where their contents were released. Collection and release of the specimens occurred in less than 1 msec. Freezing rates were estimated to exceed 3°/msec. Samples were then freeze-substituted with ethanol at −75 C for two weeks, embedded in Epon, sectioned, and stained for electron microscopy.

Up to ten biopsies of the left ventricular wall of one heart could be obtained while the heart contracted isobarically or isovolumetrically at various end-diastolic pressures. Ice crystals disrupted the ultrastructure in some areas of the sections obtained, while other areas remained virtually devoid of damage.

During isobaric contraction, changes in heart volume from end-diastole to peak systole were measured directly, and the expected change in the ratio of sarcomere length to A-band length was estimated. In some sections the observed changes in ratios agreed with the ratio change expected by volume measurements. Electron micrographs of sections obtained in the same manner but collected in 10% formalin at room temperature showed the myofibrils to be in contraction regardless of whether the sections were obtained during systole or diastole.

Simple Assessment of Left Ventricular Function During Cardiac Catheterization in Children (P)

Douglas Moore, Buffalo, New York

A simple assessment of left ventricular function may be obtained by estimation of both stroke volume and that proportion of end-diastolic volume ejected during each systole. These parameters were calculated from measurements of end-diastolic volume (Ved) and end-systolic volume (Ves) obtained during cardiac catheterization of over 50 children by selective cineangiography in the right anterior oblique projection to determine the long axes of the left ventricular cavity, correction being made for distortion inherent in the optical system. Ved and Ves were then derived

by treating the ventricular cavity as a mathematical ellipsoid. Systemic output had been determined previously by the Fick principle and by indicator-dilution curves. In the absence of large intracardiac shunts or valvular regurgitation, mean percentage differences between outputs derived from volumetric study and from indicator curves (18 cases) were 7% and from the Fick principle 10% (26 cases).

Mean stroke volume in controls was 55 ml/m² B.S.A. (SD 7 ml). It was lowered in obstructive conditions (means 43 to 46 ml/m²) and raised in ventricular septal defect with moderate pulmonary flow (mean 65 ml/m²). Significant elevations occurred with aortic and mitral regurgitation (mean 85.5 ml/m²). In these patients the degree of regurgitation was quantitated. The fraction of end-diastolic volume ejected (Ved − Ves/Ved) was 78% (SD 4%) in controls. Significant elevations were encountered in moderately severe outflow obstruction (88%), while smaller increases were found in patients with milder obstruction and with moderate left-to-right shunts.

Methods for the measurement of left ventricular volume are often complex. This simplified single-plane cineangiographic technique is accurate and especially suited to a pediatric diagnostic laboratory, adding little to the length or hazard of the catheterization. Valuable information concerning left ventricular function in children may be readily obtained.

Effects of Positive Pressure Breathing on Aortic and Vena Caval Blood Flow

Beverly C. Morgan, Wayne E. Martin, Thomas F. Hornbein, Edward W. Crawford, and Warren G. Guntheroth, Seattle, Washington

Twelve studies were performed in eight healthy dogs one to six weeks after implantation of pulsed ultrasonic flow transducers on the aorta and vena cava. Under light general anesthesia aortic and vena caval blood flow were recorded, and the systemic arterial, endotracheal, and pleural pressures were measured. Data were obtained during spontaneous respiration and using a Bird Mark 9X respirator at a constant ventilatory rate with peak airway pressures of 10, 20, and 30 mm Hg. At each pressure setting, inspiratory to expiratory (I:E) ratios of 1:2, 1:1, and 2:1 were applied. A partial rebreathing system was utilized, maintaining end-expiratory CO_2 constant; frequent measurements of arterial PCO_2 confirmed the constancy of alveolar ventilation.

Maximum values for stroke volume and cardiac output occurred during spontaneous breathing. As airway pressure was increased, aortic stroke volume and cardiac output were progressively decreased. The increase in stroke volume was somewhat compensated by tachycardia with a smaller decrease in cardiac output (stroke volume × rate). At each airway pressure, decrease in stroke volume and cardiac output was accentuated by prolongation of inspiration. At peak airway pressure of 30 mm Hg, I:E ratio of 2:1, the stroke volume was reduced 44%, while cardiac output was 33% below control. Venous return was inhibited by increasing pressure, approaching zero level with peak airway pressure of 30 mm Hg; the forward surge of vena caval flow occurred during expiration. Circulatory changes at high airway pressures were similar to those observed during cardiac tamponade.

P-Wave Analysis in the Electrocardiographic Diagnosis of Left Ventricular Hypertrophy (P)

James J. Morris, Jr., William M. Dunlap, Howard K. Thompson, Jr., Henry D. McIntosh, and E. Harvey Estes, Jr., Durham, North Carolina

The magnitude of P-wave negativity at V_1, (P_{tf}) is a sensitive indicator of hemodynamically significant valvular heart disease. Its use as a single electrocardiographic criterion in the diagnosis of left ventricular hypertrophy (LVH) was compared with other established criteria, i.e., voltage, strain, delayed intrinsicoid deflection (intrinsicoid), and left axis deviation (LAD) in 350 autopsied patients without valvular heart disease. LVH was present at postmortem in 192 cases and absent in 158. The value of P_{tf} in improving the electrocardiographic diagnosis of LVH when combined with other established criteria is also shown.

Proven LVH in the 192 patients was detected by voltage 66%, strain 56%, intrinsicoid 53%, LAD 29%, and P_{tf} 46%. LVH was falsely diagnosed in the 158 patients without this finding by voltage 35%, strain 9%, intrinsicoid 23%, LAD 9%, and P_{tf} 7%. When electrocardiographic evidence of LVH was present, it was confirmed at autopsy by voltage 70%, strain 86%, intrinsicoid 73%, LAD 79%, and P_{tf} 89%.

Since no single criterion consistently confirmed the autopsy finding, combinations were evaluated. When two of the four conventional measures, i.e., voltage, strain, intrinsicoid, and LAD were used, LVH was detected in 58% of the cases. The presence of two of all five criteria increased detection of LVH to 73%. In both situations a false positive diagnosis of LVH was made in 18%.

This study demonstrates the sensitivity, the number of false positives, and selectivity of five electrocardiographic criteria for LVH. The use of P_{tf} in combination wth other criteria significantly improves the electrocardiographic recognition of LVH.

Epidemiology of Rheumatic Heart Disease in Colorado (P)

William E. Morton, Denver, Colorado

High altitude and low humidity have been suggested as causative factors responsible for the Rocky Mountain area's reputation as a high-risk region for rheumatic fever (RF) and for rheumatic heart disease (RHD).

RF and RHD mortality data for the nation and for Colorado suggest that factors other than physical geography may be involved. Altitude was unrelated to RF incidence or mortality or to RHD mortality in Colorado. These indices all indicated a particular region, the San Luis Valley, as one of particularly high risk. The San Luis Valley is the most economically depressed area in Colorado.

Extensive studies of RHD prevalence in school children in Denver and in the San Luis Valley and in Colorado's Selective Service records have provided an excellent basis for characterization of the distribution of RHD by age, sex, ethnic group, socioeconomic status, and geographical features in Colorado.

The available evidence suggests that Colorado's geography has relatively little effect on RHD occurrence within the state and that the most important factors are socioeconomic status, ethnic background, and age of the individual at risk.

Studies of Clotting and Fibrinolysis Across the Heart: Response to Catecholamine Infusion (P)

Christos B. Moschos, Patrick H. Lehan, Henry A. Oldewurtel, and Gabriel T. Koroxenidis, Jersey City, New Jersey

It has been shown that during coronary thrombosis the clotting activity of the coronary sinus (CS) blood increases, whereas its fibrinolytic activity decreases. Although they increase coronary flow, catecholamines induce myocardial metabolic changes similar to those observed after coronary thrombosis. This observation led to an investigation of the fibrinolytic and clotting response of the myocardium following sustained intracoronary infusion of epinephrine. In ten closed-chest anesthetized dogs, the CS, circumflex coronary artery, and aorta were catheterized. Epinephrine (5 μg/min for 90 minutes) was constantly infused into the circumflex coronary artery. Samples from the aorta and the effluent of the infused area (CS) were taken in plastic "glassware" prior to and at 15 to 20, 30 to 45, and 90 minutes during epinephrine infusion. The results are expressed as per cent change of control values. In CS the thromboplastin generation test, expressed as time required for 50% yield, accelerated 150% in the 30- to 45-minute samples. Glass and plastic tube clotting times decreased 40% and 75%, respectively. The euglobulin lysis time was accelerated 50% at 30 to 45 minutes and was followed by a prolonged lysis time at 90 minutes. Platelet counts and fibrinogen levels did not show consistent changes in either direction. The changes in the aortic samples followed those of the CS but were of less magnitude. The data suggest that significant regional changes in fibrinolytic and clotting activity can occur as the result of circulating catecholamines, even in the presence of an increased blood flow. The anatomical and hemodynamic peculiarities of the coronary arteries which may predispose to vascular damage, in combination with the demonstrated effects of catecholamines on clotting and fibrinolysis across the heart, might explain the higher incidence of thrombosis in the coronary vessels.

Effect of Corticosteroid on the Acidosis of Prolonged Cardiopulmonary Bypass (P)

Melvin L. Moses, Rudolph C. Camishion, Kouichi Tokunaga, Louis Pierucci, Jr., and Allen L. Davies, Philadelphia, Pennsylvania

Metabolic acidosis is a common complication of prolonged cardiopulmonary bypass. This appears to be due to anerobic glycolysis, as evidenced by a rise in excess lactates. Corticosteroids are believed to affect certain enzymatic reactions of intermediate carbohydrate metabolism; however, the exact mechanisms are not known. In these experiments low flow rates, which consistently produce severe metabolic acidosis, were used. Corticosteroids were administered to determine their effect.

Ten control dogs were placed on total normothermic cardiopulmonary bypass for two hours at a flow rate of 50 ml/kg of body weight. The flow rate, central arterial and venous pressures, and body temperature were continuously monitored. The pH, pO_2, pCO_2, hematocrit, lactic and pyruvic acids, excess lactates, and total buffer base were measured before perfusion, at half-hour intervals during the bypass, and thereafter. Ten other animals were treated identically except that corticosteroid, 50 mg/kg of body weight, was given intravenously two hours before bypass.

All control animals developed severe metabolic acidosis with the pH averaging 7.10. Excess lactates averaged 4.2 mM/L. The animals pretreated with corticosteroids maintained an average pH of 7.30. Excess lactates averaged 3.0 mM/L.

After bypass the untreated animals could not maintain an adequate arterial pressure and failed to react, and all died. The pretreated animals maintained a normal arterial pressure after bypass,

reacted promptly from anesthesia, and survived the operation without difficulty.

In these experiments corticosteroid administration maintained pH, decreased metabolic acidosis, and markedly increased survival. Several possible explanations for these phenomena are presented in the report.

Cardiovascular Dysfunction During Sustained Norepinephrine Infusion

Arthur J. Moss‡ and Eric Schenk,‡ Rochester, New York

Sustained infusions of *l*-norepinephrine (NE) are frequently used in the treatment of cardiogenic shock, and the purpose of this study was to evaluate the hemodynamic changes during prolonged NE infusion and the mechanisms of the NE effects. Varying doses of NE (1, 2, and 4 μg/kg/min) were infused intravenously for four hours into 15 anesthetized dogs; five dogs served as controls. During the baseline state and at selected intervals during the NE infusion, measurements were made of the left ventricular pressure (LV), the first derivative of LV (dp/dt), systemic pressure (SA), cardiac output (CO), blood hematocrit (Hct), arterial pH, hemoglobin saturation (% SaO_2), serum lactic dehydrogenase cardiac isoenzyme activity (LDHc), and I^{131} blood volumes (BV). At the conclusion of each study, autopsy examinations were performed.

After an initial increase in SA, CO, and dp/dt during the first 15 minutes of NE infusion, at all dose rates there was a progressive deterioration in SA, a marked decline in CO, and a sustained increase in dp/dt and the peripheral vascular resistance (PVR). After three hours of NE, a significantly negative inotropic state developed (Starling curve) in association with electrocardiographic Q waves and an increased LDHc. Hct increased during all NE infusions, but there was no significant change in BV, pH, or % SaO_2 when compared with the control group. Autopsy studies revealed dose-related myocardial hemorrhages, scattered loss of myocardial oxidative enzymes, myocardial lipid accumulation, and myofiber necrosis. In conclusion, the dysfunctional effects of prolonged NE infusion consist of an increased PVR and a negative inotropic state associated with destructive myocardial lesions.

Second-Year Follow-up of Exertional Myocardial Ischemia in "Healthy" Middle-aged American Men

Albert S. Most, John A. Mazzarella, Donald R. Peterson, and Robert A. Bruce, Seattle, Washington

The Seattle Y.M.C.A. prospective study is utilizing electrocardiogram-monitored maximal exercise testing of "healthy" middle-aged men in an attempt to identify individuals with preclinical or potential ischemic heart disease. The third annual examination now includes a computer technique for quantifying electrocardiographic parameters during rest and exercise. A computer of average transients averages voltage of 100 consecutive electrocardiographic signals in each stage of the treadmill test. This increases the signal-to-noise ratio, rendering previously unusable exercise records adequate for analysis. Quantification of ST-segment depression eliminates reader variability and provides a statistical distribution separating "normal" from "abnormal" electrocardiographic responses.

ST-segment elevation or depression is measured relative to the most stable 0.02-second segment of the PQ interval. Utilizing the sixth 0.01-second interval following the S nadir provided the following values: 0.066 ± 0.049 mv elevation at rest (n 45); 0.091 ± 0.095 mv depression at maximal exercise (n 44); 0.026 ± 0.067 mv elevation during the initial period of recovery (n 45).

Preliminary data indicate the flat or downsloping ST segments at rest correlate with depth of ST depression in initial recovery. Twelve such subjects had a mean postexercise ST change of -0.026 ± 0.052 mv, whereas 32 with positive resting ST slopes had an elevation of $+0.040 \pm 0.057$ mv ($P < 0.001$).

Seven (11%) of the first 62 men re-examined to date continue to exhibit segmental ST depression after exercise greater than 1 mm on visual interpretation. One individual's response reverted to normal.

Mean cholesterol and triglyceride values in 53 men were 222 mg% and 81 mg%, respectively.

Diagnostic and Physiological Implications of the Angiotensin Infusion Test (P)

Spero E. Moutsos, Eliseo Perez-Stable, and Alvin P. Shapiro, Pittsburgh, Pennsylvania

The angiotensin infusion test (AIT), suggested by Kaplan, to differentiate hypertension with and without renal artery stenosis (RAS) was evaluated. Forty-six hypertensive patients were studied; 20 had RAS demonstrated by aortography. Thirteen normotensives were similarly tested. Angiotensin (0.004 μg/kg/min) was infused for five minutes; after a second baseline 0.03 μg/kg during one minute was given.

Results were expressed as calculated mean blood pressure (MBP) but were similar if diastolic blood pressure was used. Normotensives rose 16.3 mm Hg $\pm$ 1.8 (SE) to the first dose and 30.3 mm Hg $\pm$ 2.2 to the second. In patients without RAS, responses were 33.4 $\pm$ 2.0

and 47.1 ± 2.9, first and second doses respectively ($p = 0.01$ for both tests). With RAS, responses were 22.8 ± 2.2 and 33.9 ± 3.7, which were less than the "non-RAS" group ($p = 0.01$) but not different from the normotensives. Thus, AIT differentiated hypertensives with RAS as a group, but individuals showed discrepancies. Malignant hypertensives with RAS (five) and without RAS (four) had similarly decreased responses. In several patients with diminished response to the low dose, hyperreactivity was "unmasked" with the larger dose, previously shown to cause greater responsiveness in primary hypertensives than in normotensives. In four patients with RAS, eledoisin, a polypeptide which "counteracts" angiotensin, did not cause a distinctive blood pressure reduction, compared to subjects without RAS.

The AIT offers additional screening for RAS but, in our experience, cannot replace other clinically indicated diagnostic and predictive studies. Response to exogenous angiotensin in RAS indicates loss of the usual hyperreactivity of hypertensives but may not simply imply that increased endogenous angiotensin is present.

Identification and Management of Exit Block in Patients with Implanted Pacemakers

Frank M. Mowry, Richard D. Judge, Thomas A. Preston, and Joe D. Morris, Ann Arbor, Michigan

Exit block, the inability of an impulse to leave its point of origin within the myocardium, was the second most common cause of failure in a series of 118 pacemaker implantations (15 instances or 13%). It was diagnosed electrocardiographically by identifying a normal stimulus artifact with a normal rate in the absence of myocardial response.

Analysis of these cases disclosed that (1) serum electrolytes were normal in all, (2) 13 had had previous cardiac surgery, and (3) onset of block in 13 occurred within the immediate postoperative period (two weeks). There was no apparent correlation with age, underlying disease, or site chosen for implantation.

Nine of 11 patients treated with prednisone, 40 to 60 mg daily, became responsive within 72 hours. Five of these are still pacing on maintenance doses of 10 mg daily. Four have required reimplantation despite drug therapy. In these and in two additional cases, the implantation site was found to be fibrotic and/or necrotic. The removed pacemakers (General Electric Company), however, proved to be in perfect working order on careful testing.

Myocardial resistance, estimated in five patients before and after steroid therapy, showed a significant decrease in three and no change in two. Threshold estimated in all nine patients fell to below 45 microjoules in each instance.

These observations suggest that corticosteroid therapy may be of value in the treatment of exit block, at least as a temporary measure. The mechanism of action is under study.

Pulmonary Pulse Pressure in Mitral Insufficiency

J. Gerard Mudd and Phillip W. Carr, St. Louis, Missouri

Thirty cases of mitral insufficiency exemplified by a high V wave in the left atrium have been studied by Radner suprasternal puncture. The pulmonary artery pressure and left atrial pressure were recorded and compared with the pattern seen in pure mitral stenosis and the combination of stenosis with insufficiency.

In pure mitral insufficiency the systolic peak of the V wave was found to be similar to the pulmonary systolic pressure, so much so that both systolic peaks are often identical and usually within 10 mm Hg of each other. When the diastolic Y point and mean pressure of the left atrium are low, so also is the diastolic pressure in the pulmonary artery. However, when mitral stenosis of any degree is superimposed, the Y point and the mean pressure of the left atrium are elevated, and the pulmonary pulse pressure is narrowed.

The presence of a wide pulse pressure in the pulmonary artery, in addition to the typical V and Y pattern found in the left atrial pressure curve, is further evidence of pure mitral insufficiency. Pulmonary vascular resistance, therefore, would seem to play a minor role in the production of the high systolic pressure, being merely a reflection (pressure wave phenomenon) of the high left atrial V wave. Pulmonary pressures would be expected to return to normal with correction of the mitral insufficiency.

Renal Hemodynamic and Metabolic Responses to Vasodilatation in Hemorrhagic Hypotension

Gerald P. Murphy, Donald W. Benson, and Horst K. Schirmer, Baltimore, Maryland

Renal responses to hemorrhagic hypotension (HH) have long been viewed as critical reflection of successful or injurious vascular responses. Thirty-seven experiments were performed on dogs to measure directly the renal hemodynamic and metabolic responses to HH at mean aortic blood pressure of 50 mm Hg for periods of 45 minutes to five hours. Chlorpromazine (0.1 mg/kg/iv) vasodilatation was achieved before or during HH or with reinfusion of shed blood.

Dogs responded to HH of 45 minutes to two hours with a 62% reduction in directly measured renal blood flow (DRBF), cessation of urinary

flow (V), loss of renal venous pressure (RVP), and an 86% rise in renal resistance (RR). Simultaneous Warburg measurements demonstrated a decrease of cortical respiration and variable increases of medullary glycolysis. Continuance of HH (five hours) resulted in progressive reduction of cortical respiration. Drug treatment before, during, or after HH decreased RR, transiently elevated DRBF, and restored V. Augmentative metabolic adjustments were limited to increases in medullary glycolysis. Blood reinfusion and chlorpromazine together failed to have additive renal effects. In prolonged HH (five hours), drug pretreatment alone was of only transient hemodynamic merit and without detectable metabolic benefit. The adrenolytic effect of chlorpromazine at the dosage used was confirmed by the abolition of the alpha-pressor response to 1 mg/kg/iv epinephrine.

A renal vasodilating agent with adrenolytic effect thus appears to be of benefit in averting characteristic renal hemodynamic and metabolic responses to hemorrhagic hypotension, but only if used early in its course.

Discrimination of Ventricular Hypertrophy Based on Correlated Structure Analysis of the Vectorcardiogram (P)

Alexander J. Muster, Merl L. Kardatzke, and Milton H. Paul, Chicago, Illinois

Methods were developed to analyze existing vectorcardiographic (VCG) data and find valid statistical indicators of pediatric ventricular hypertrophy patterns. A well-defined, efficient data encoding system was based on hand measurements of the x, y, z coordinates of the extreme points and the initial and terminal inflection points of the planar vector loops. The cumulative distance through the spatial vector loop (D coordinate) was used to indicate the sequence and spacing of these points. Factor analysis was used to summarize the correlated structure of the normals, and discriminant functions were found to maximize group separation. In all, 665 individual VCG were analyzed: normals (N), aged one day to 19 years, 217 cases; right ventricular hypertrophy (RVH) represented by tetralogy and pulmonary stenosis, 105 cases; left ventricular hypertrophy (LVH) represented by aortic stenosis, 65 cases; combined ventricular hypertrophy (CVH) represented by ventricular septal defect, 50 cases, patent ductus arteriosus, 44 cases, and tetralogy with shunt, 184 cases.

Discrimination between normals and pediatric hypertrophy groups resulted in about 90% correct classification. Aortic stenosis (LVH) was the most difficult hypertrophy group to separate from normals. The magnitude of the maximum spatial vector was the most important variable for separation of LVH from N, and it was also important for discriminating CVH from N. The x coordinate of the right extreme point was the most useful variable in discriminating RVH from N, CVH from N, and CVH from LVH. The D coordinate of the left extreme point is the most important variable for discrimination of CVH from RVH. Other important discriminant variables include the x and z coordinates of the posterior extreme point and the x coordinate of the maximum spatial vector. The methods described provide quantitative characterization of the VCG by shape and magnitude and permit statistical discrimination of pediatric ventricular hypertrophy groups.

Organ Abnormalities Associated with Congenital Cardiac Malformations

Richard L. Naeye, Burlington, Vermont

Many children with congenital cardiac malformations have unrecognized abnormalities in other organs. A total of 140 children consecutively admitted with congenital cardiac malformations had birth weights on the mean 12% below expected values for gestational age. By means of line sampling, planimetry, and other quantitative histological methods, 18 such infants dying in the perinatal period were found to have a subnormal number of morphologically normal cells in most body organs. The reduction varied from organ to organ and from case to case. In many respects, these abnormalities resemble those associated with fetal rubella and with certain congenital chromosomal abnormalities.

Also examined were 24 infants with cardiac malformations who had died after gaining little weight in the one to five months since their birth. Cells in their organs were not only subnormal in number but had a marked reduction in cytoplasmic mass, some organs and cell types being more abnormal than others. The particular pattern of tissue abnormalities observed in these infants closely resembles that found in infants dying with alimentary malnutrition. Dietary intake had been normal in some of the infants with cardiac malformations and subnormal in others. Retarded brain development was evident in the cardiac group and suggests possible new criteria for selecting cases for corrective surgery. Specific structural abnormalities in the pituitary, pancreas, and liver suggest bases for functional disturbances in these organs. The organ abnormalities indicate bases for the growth retardation often observed in infants with congenital cardiac malformations.

Experimental Valvular Endocarditis Following Parabiosis (P)

Komei Nakao, Masamichi Oka, and Alfred A. Angrist, New York, New York

Twelve Novikoff tumor-resistant rats (rats with regression of tumor implantation with subsequent survival) were parabiosed to intact rats, with a similar number of parabionts of intact-intact rats as parabiotic controls. Other groups consisted of a similar number of tumor-carrying rats and of intact normal rats of same weight. The tumor-resistant parabiotic pairs developed marked, even startling, changes in the heart valves, particularly in the tricuspid and the mitral, and marked adrenal hypertrophy. The dramatic valvular lesions developed within one to two weeks after parabiosis and showed an extensive cellular reaction in the subendothelial stromal tissue, associated with marked edematous swelling. The changes occurred only after the seventh to eighth day with progressive disarray of collagen bundles, histiocytic cell reaction, fibrinoid changes, and platelet vegetation on the surface with the ultimate result being marked alteration of the valves. The relationship of the factors of tumor growth and tumor regression to the valvular lesions is not understood. The phenomenon of rejection of the total animal, considered as a massive graft, and of runt disease to high levels of ACTH in proportion to corticosteroids, as revealed by adrenalectomy, in parabiotic rats were considered in relation to the valvular changes.

Susceptibility of the Lathyritic Rat to Endocarditis (P)

Ryuichi Nakayama, Lucille A. Gronkowski, and Raymond C. Read, Detroit, Michigan

Recent clinical experience has emphasized the frequency of both insufficiency from myxomatous valvular transformation and secondary endocarditis in the aortic and mitral valves of patients suffering from Marfan's syndrome or its many *formes frustes*. The purpose of the present study was to determine whether a similar phenomenon could be demonstrated in an experimental analogue, the lathyritic rat.

Eight 21-day-old rats given lathyrogen (0.4% beta-aminopropionitrile fumarate, BAPN) in their diets began to develop limping, kyphoscoliosis, and pectus carinatum three weeks later. Aortic dissections subsequently developed in four. Another 16 rats, lathyrized with 0.4% or 0.3% BAPN, were injected intravenously on the twenty-first diet day with 4×10^8 *Streptococcus viridans* organisms. Blood cultures were drawn at intervals. Fifty per cent became positive before sacrifice at two weeks. At postmortem examination vegetations on the aortic or mitral leaflets were identified histologically in 50%. Comparable control groups had negative blood cultures and no lesions discernible on the leaflets. Microscopically, a myxoid change in the valvular architecture was apparent in the lathyritic animals. The results of a similar group of rats treated with 0.2% BAPN and injected with bacteria demonstrated an increased susceptibility of the heart valve to infection in lathyrism. These experimental findings suggest that the observed tendency to endocarditis found in patients with myxomatous valvular transformation is a reflection of their mesodermal dystrophy.

Abnormal Venous Return in Patients with Hyperinflation of the Lungs

Fred N. Nakhjavan, Wilfred H. Palmer, and Maurice McGregor, Montreal, Quebec, Canada

In some emphysematous patients there is an abnormal, inspiratory reduction in the forward velocity of blood flow in the inferior vena cava (IVC). Because of the difficulty of interpreting such data, the observations were extended to determine what pressure gradients may result from this phenomenon. Venous return to the heart was studied in 15 subjects with pulmonary emphysema. Respiratory changes in flow were determined by measuring changes in transmural pressure of right atrium (RA) and IVC. These were determined by simultaneous recording of respiration, RA pressure, esophageal pressure, IVC pressure, and gastric pressure. Cineangiograms of IVC were obtained and correlated with transmural pressure studies. Normally, during inspiration, because of increased flow into RA, there is an increase in RA transmural pressure and a decrease in IVC transmural pressure. Nine of these patients had normal venous return at rest. Six subjects had an abnormal pattern which consisted of a decrease in flow during inspiration and an increase during expiration. There was thus a mechanical hindrance to forward flow when the intrathoracic pressure was most negative. Consequently, the second heart sound was paradoxically split, and the mean IVC pressure was increased. In patients not showing this phenomenon during quiet breathing, it could be brought on by forced deep inspiration. This restriction to venous return which could be demonstrated in some emphysematous patients without evidence of pulmonary hypertension or right-sided heart failure appears to be a previously undetected cause of circulatory embarrassment.

Ectopic Cardiac Response to Electrical Stimulation

David A. Nathan, Aaron Medow, and Raul Pina, Miami Beach, Florida

Since the introduction of idioventricular pacemaker therapy for the treatment of complete heart

block and Adams-Stokes syndrome, doubt has existed regarding the potentially harmful effects of electrical stimulation during the vulnerable period of the cardiac cycle. Most observers are of the opinion that such stimuli are harmless, while others have recently documented the initiation of serious rhythm disorders in man. In an effort to resolve the problem, animal studies were undertaken. A Cordis synchrocor was used to apply a synchronized 2-msec biphasic pulse wave during the vulnerable period of the cardiac cycle by means of direct atrial and ventricular electrodes. Stimulus magnitude was varied from 0.1 to 17 ma. Synchronous stimuli were applied during normal and graded decrements of oxygen saturation and after circumflex coronary artery occlusion. These studies revealed that (1) repetitive ectopic systoles and tachycardia are easily producible; (2) hypoxia to the range of 60 to 70% produces some reduction of threshold excitability but is markedly affected by circumflex arterial occlusion; (3) the stimulus magnitude required for sustaining ectopic beats and tachycardia is less than that necessary for initiation; (4) the vulnerable period can be shifted in the direction of the ST interval by repetitive stimulation following arterial occlusion. It is concluded that experimentally produced low threshold states are vulnerable to single and repetitive response in dogs by stimuli of the magnitude and duration of contemporary idioventricular pacemakers.

Estrogenic-like Activity of Digitalis (P)

Ali Navab, Leopold G. Koss, and John S. LaDue, New York, New York

Fifty-two postmenopausal patients receiving glycosides for heart disease were evaluated at Memorial Center. Routine vaginal and cervical smears were obtained and stained with the Papanicolaou stain. In the presence of infection, the patient was treated accordingly, and the cytology studies were repeated.

The cytology studies on 52 postmenopausal women taking 0.1 to 0.2 mg of digitoxin daily for three months to 15 years and 50 control postmenopausal women were read by two pathologists who were purposely given none of the clinical background.

Twenty patients who had been receiving cardiac glycosides for more than two years exhibited marked cornification of the vaginal squamous epithelium. None had taken estrogen or other hormones, yet the patients showed evidence of a "distinctly elevated estrogenic level." Eight of these patients had cytology studies prior to digitalis intake which were reported as "atrophic; no estrogenic effect." After two years of digitoxin, maturation of the squamous epithelium developed.

The 30 postmenopausal women who had been taking cardiac glycosides less than two years failed to show significant cornification of the vaginal epithelium. The control smears from 50 postmenopausal women not receiving cardiac glycosides were atrophic. The cytology of only two patients who had been taking digitoxin less than two years showed high cornification of the vaginal epithelium.

The estrogenic-like effect of digitalis may convert a normal, atrophic, postmenopausal vaginal smear to one suggesting an abnormal estrogen effect. Abnormally increased squamous maturation may be the first clue to endometrial carcinoma. Some of our patients had episodes of slight vaginal bleeding, and the combination of vaginal spotting and high squamous maturation in a postmenopausal woman would be suggestive of endometrial or ovarian carcinoma.

Effect of Myocardial Contraction Rate on Myocardial Metabolism in the Isolated Dog Heart and in Human Subjects

William A. Neill, Portland, Oregon

In previous experiments with the isolated dog heart, decrease in the O_2 concentration of coronary venous blood, caused by diminished coronary blood flow or arterial hypoxemia, resulted uniformly in a rise in the lactate/pyruvate concentration ratio of the coronary venous blood, indicating hypoxia of the myocardial tissue. The purpose of the present experiments was to determine whether decrease in coronary venous blood O_2 concentration caused by increase in metabolic requirements of the myocardium, rather than decrease in its O_2 supply, is also accompanied by the rise in lactate/pyruvate ratio.

Metabolic rate of the isolated heart was increased by augmented contraction frequency. When coronary blood flow was held constant, the increase in myocardial O_2 utilization caused a fall in coronary venous blood O_2 concentration. In contrast to the ischemia and hypoxemia experiments, however, the coronary venous blood lactate/pyruvate ratio often did not rise, suggesting that with tachycardia the fall in O_2 concentration in the coronary venous blood did not always indicate hypoxia of the myocardium.

In normal human subjects increase in heart rate induced by atropine or direct electrical stimulation did not change either the O_2 concentration or the lactate/pyruvate ratio of coronary venous blood. Thus, there was no evidence of myocardial hypoxia. On the other hand, in some patients with coronary disease, tachycardia did cause a rise in coronary venous lactate/pyruvate ratio, the increase in myocardial energy requirements apparently resulting in myocardial tissue hypoxia.

Lead System for Direction and Magnitude of the Heart Vector

Clifford V. Nelson, Portland, Maine

The new system is based on the integration theory, which states that the resultant dipole moment of a system of current sources and sinks inside a volume conductor can be found from a surface integration of potential over the outer boundary.

The method uses three rows of eight equally spaced electrodes. The levels of the rows are determined relative to the umbilicus and the suprasternal notch. The vertical component is found by the foot-head lead, corrected for the appearance of voltage due to the Z component of the dipole in this lead. The integration is done approximately by a resistance network, so that the cardiologist has only to apply the electrodes to the body and the output leads to the X, Y, and Z amplifiers and adjust the gains of the amplifiers.

The system has been tested by artificial dipole experiments in an accurate plexiglass model of the human thorax, as well as by comparisons with complete integrations on humans and animals. The agreement has been found to be good with respect to both magnitude and direction of the heart vector.

Fate of Teflon Vascular Grafts (P)

Paul Nemir, Jr., Donald E. Wagner, Fred M. Honigman, and Anthony V. Dapena, Philadelphia, Pennsylvania

During the past ten years we have operated on approximately 295 patients with aneurysms of occlusive disease of the aorta and great vessels. Treatment has been by endarterectomy, some type of plastic procedure, and/or replacement or bypass graft. Sixty-five per cent, or 192, have had insertion of a prosthesis.

Late complications of thrombosis and/or false aneurysm formation in five patients, necessitating multiple graft replacements, have afforded the opportunity to study the long-term fate of patent woven Teflon prostheses implanted for up to three years. A total of 13 replacements have been carried out in the five patients, and in three it was possible to study the fate of Teflon implanted at different times in the same individual. Serial sections from long grafts have allowed a clearer understanding of the formation of the inner lining and the contribution of the blood components.

Pluripotential reticuloendothelial cells form on either side of the Teflon prosthesis. These cells come from the blood and from the fixed store of histiocytes in the tissue. The inner lining of the Teflon is composed of a layer of large foreign body type reticuloendothelial cells immediately adjacent to the graft; a layer of variable thickness of amorphous, practically cell-free, fibrin; and a single layer of cells, probably monocytes, which clearly represents an attempt at intima formation. This study affords a comparison with recent information on the long-term fate of Dacron prostheses.

Transvenous Pacing of the Heart (P)

Henry N. Neufeld, D. Goor, D. Nathan, Tel-Hashomer, Israel, S. Leibinsohn, England, and E. Frei, Tel-Hashomer, Israel

There are some emergency cases in which electronic pacing of the heart is a life-saving procedure. The methods in use are external pacing, intracardiac catheter pacing, and percutaneous pacing. The most commonly used and most effective method is the intracardiac catheter pacing. This method, however, is limited to the catheterization room, and another disadvantage is the inability to fix the electrode to the heart muscle.

A new method of intracardiac pacing is presented which can be carried out without fluoroscopy and which enables fixation of the electrode to the heart muscle. A short polyethylene catheter with an internal lumen of 3 mm is introduced via a peripheral vein into the vena cava. A magnetic "POD" which is connected by a flexible electrical wire to a pacemaker is introduced via this catheter into the vena cava. From the lumen of the vena cava, the "POD" is carried by the blood stream like an embolus into the right ventricle. Outside the chest, opposite the right ventricle, a magnetic field is induced. When the "POD" reaches the right ventricle, it becomes attached to the ventricular wall due to the magnetic force, and pacing is automatically initiated.

Complete atrioventricular block was surgically produced in six dogs. At a later stage, under anticoagulant cover, transvenous pacing catheterization, as described above, was performed. Uninterrupted pacing was demonstrated.

Estimation of Fasting Serum Triglycerides by Determining Low Density Lipoprotein Cholesterol

Milton Z. Nichaman, Ksenia M. Tomitch, and Esther J. Allen, San Francisco, California

In recent years interest has developed in the relationship of serum triglyceride levels to the incidence and prevalence of coronary heart disease. Few studies on the distribution of triglyceride values in large population groups have been reported because of the large differences between fasting and nonfasting triglyceride levels coupled with

the difficulty of obtaining fasting samples. This study was designed to test a method which would give a good estimate of fasting triglyceride levels in nonfasting, randomly collected specimens. Fasting and randomly collected nonfasting blood samples were obtained from 40 subjects. Total serum cholesterol and serum triglyceride concentrations were determined in each sample. In addition, each blood sample was spun in an ultracentrifuge for 30 minutes at 30,000 rpm at a density of 1.006. The top layer was removed, and the amount of cholesterol was determined in this very low density lipoprotein fraction (VLDLP). In agreement with previous studies, the correlation between fasting cholesterol and triglyceride levels was of a very low order. A high order of correlation was found between the level of cholesterol in the VLDLP fraction of the nonfasting samples and the level of fasting serum triglycerides. The correlation between fasting and nonfasting triglyceride levels was appreciably lower. On the basis of these studies, we feel that the measurement of cholesterol in the VLDP fraction of nonfasting blood samples will give a valid estimation of the level of fasting serum triglycerides. Utilization of this technique would greatly facilitate the investigation of serum triglyceride levels in large population groups.

Indications for Valve Replacement in Mitral Surgery: Experience with 659 Open Operations, 1958 to 1965 (P)

Henry T. Nichols, Dryden P. Morse, Gumersindo Blanco, Alberto Adam, and Sariel Ablaza, Philadelphia, Pennsylvania

Since 1958, the authors have performed 225 operations (open) for predominant mitral insufficiency. With only fair long-term results from annulus plications, the indications for valve replacement have gradually been liberalized until at the present time 90% of patients with mitral regurgitation have prostheses inserted. Plastic repair, however, is still done for some patients with torn leaflets, ruptured chordae, etc., in whom the absence of severe calcification or severe annulus dilatation makes possible the reconstruction of a permanently competent and efficient valve.

In September, 1959, the authors abandoned closed-heart operations for all patients with mitral stenosis. Since then, 434 open operations have been done (to January, 1965). A superior valve repair has been possible under direct vision, especially with respect to opening both commissures fully, relieving subvalvular stenosis, removing loose calcium from the valve, and repairing minor valvular insufficiency. Easy removal of unsuspected atrial thrombus has been an additional benefit of the open technique. In pure mitral stenosis only severe calcification and fibrosis necessitate valve replacement (in 10 to 15% of patients at this time). In 137 cases in which the Starr-Edwards prosthesis has been inserted (in 659 open mitral valve operations), operative mortality has been 19%, and late deaths have brought total mortality to 25%. Clinical application of an improved caged-ball prosthesis designed to prevent late thrombosis and embolism is described in the report.

Vibration Transmission Between Heart and Ballistocardiograph (P)

John L. Nickerson, Henry Pevsner, Richard Johnson, and Herbert Udesen, Chicago, Illinois

Research in ballistocardiography has led gradually to the acceptance of the ultra-low frequency ballistocardiograph as having the most desirable characteristics. This decision has not been based on a direct study of the purity of transmission of mechanical impulses between the heart and the ballistocardiograph. The present research was directed toward this particular problem.

A radiopaque plaque was sutured on the heart of a dog. The anesthetized dog was fastened rigidly in the cradle of the ballistocardiograph. The suspension of the ballistocardiograph was mounted on a sinusoidal oscillator of variable amplitude and frequency. Sinusoidal motion of the oscillator produced periodic motions of the ballistocardiograph system and of the opaque implant. The opaque object in a beam of X-rays appeared as a shadow having sinusoidal oscillation. When this shadow fell on a horizontal slit in a lead screen placed in front of a photographic film and when the photographic film was moved vertically at uniform velocity behind the slit, the shadow of the opaque object made a sinusoidal trace on the film. Simultaneous records of opaque object, ballistic cradle, and sinusoidal oscillator permitted determination of amplitude transfer functions and phase changes on transmission of motion through the body from oscillator to heart. The results demonstrate that the ultra-low frequency system has acceptable characteristics.

Relationship of Coronary Blood Flow and Cardiac Performance to Regurgitant Flow in Acute Experimental Aortic Insufficiency

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The severity of aortic insufficiency (AI) can often be correlated with the amount of regurgitant flow through the aortic valves. It is unresolved, however, if this change in systemic hemodynam-

ics leads to an increase or a decrease in coronary blood flow (CF) which may affect ventricular performance. Therefore, along with total stroke volume (SV), regurgitant flow, and net SV, CF was determined in various degrees of reversible AI. In 12 dogs flow was measured in the ascending aorta and in one of the main branches of the coronary arteries with an electromagnetic sine-wave flowmeter. In acute aortic regurgitation up to 50% of total SV, no directional change in CF/stroke could be observed. However, when regurgitant flow reached more than 60% of total SV, the CF decreased, even though left ventricular peak pressure and tension-time index rose or stayed constant. In addition, the CF inflow pattern changed markedly with the systolic portion increasing while diastolic and total CF were reduced.

It is concluded that a diminished CF at a time of high cardiac oxygen demand may lead to coronary insufficiency. Thus, the observed elevation in left ventricular end-diastolic pressure in acute AI may in part be attributed to heart failure due to coronary insufficiency and is not solely due to the increased diastolic filling by aortic regurgitation.

Role of the Calcium Ion in Interval-Dependent Myocardial Contractility Changes

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The effect of calcium on the contraction height of isolated, perfused rat hearts stimulated with different rates (1 to 6/sec) and/or paired impulses was investigated. At normal calcium level (2.6 mEq/L), steady state contraction height is approximately proportional to the stimulation rate and can be increased still further by paired stimulation. At a high calcium level (8.4 mEq/L), contraction height is the same and maximal at each heart rate and cannot be increased further by paired stimulation. At low calcium level (1.6 and 0.5 mEq/L), the contraction height is far below normal, but the rate of increase of contraction height at progressively higher frequencies is greater than normal. Paired stimulation counteracts the contractility-depressing effect of low calcium perfusion.

With respect to the contractile response of the heart, the effect of different calcium concentrations in the perfusion fluid at fixed heart rate (2.5/sec) can be substituted for the effect of different heart rates at constant calcium concentration (2.6 mEq/L). The contraction height increases under both circumstances, but the oxygen consumption of the heart per beat remains constant, while increase in contraction height originated by norepinephrine at constant stimulation rate increases the oxygen consumption per beat. From these results it is concluded that contractility changes originated by interval changes are regulated by the calcium ion.

Intraluminal Pressure-Sealing Grafts for the Repair of Arterial Wall Defects (P)

John D. Nofzinger, Thoralf M. Sundt, and Francis Murphey, Memphis, Tennessee

A technique was developed for rapid repair of arterial wall defects in arteries ranging from 2.5 to 4 mm in diameter without luminal compromise.

Thirty-six arteriotomy wedge defects, 0.5 cm long and from one-fourth to one-third of the circumference of the artery in width, were made in the femoral or carotid arteries of adult mongrel dogs. A clip fashioned from a multiperforated siliconized tube lined with autogenous vein was applied over the arteriotomy defects. Vector forces of the arterial pressure sealed the arterial wall against the autogenous vein around the periphery of the arteriotomy defect. The siliconized clip prevented the vein graft from being displaced by the arterial pressure.

Of the 36 grafts installed, the last consecutive 33 were patent. The grafts were serially removed over a six-month period and evaluated by means of arteriography and serial histological section for patency, percentage of luminal compromise, rates of re-endothelialization, foreign body reaction, false aneurysmal formation, and calcification in the graft. In all 33 grafts the luminal compromise was less than 5%. Re-endothelialization was noted to be complete by the seventh day. Fibrosis, scar, and foreign body reaction were minimal to absent in all grafts. At the end of six months, no false aneurysmal formation or calcification of the grafts was noted.

Such a technique may be applicable to the repair of intracranial vessels from which an aneurysm has been torn off, as well as to coronary arteries subjected to surgical arteriotomy for the purpose of embolectomy or endarterectomy.

Circulatory Responses to Small Doses of Angiotensin II

John P. Nolan and Leonard A. Cobb, Seattle, Washington

Circulatory responses to the administration of very small doses of angiotensin were examined in 22 subjects: six normals, nine with arterial hypertension, five with valvular heart disease, and one each with coronary atherosclerosis and cirrhosis. Constant intravenous infusion of 4.5 to 19.0 (mean 8.0) μg/kg/min (0.5 μg/min) had no signifi-

cant effect on cardiac output (−0.02 L/min/m²) or heart rate (+1 beat/min). Infusion rates were adjusted for each individual to approximate the lowest dose producing a 20-mm Hg pressor response. Mean arterial pressure (MAP) rose 24 mm Hg and diastolic pressure 18 mm Hg. Changes in estimated hepatic blood flow (EHBF) were calculated from changes in the rates of disappearance of indocyanine-green dye (ICG) from the plasma after a sudden injection of the dye. In nine subjects a hepatic vein was catheterized and hepatic extraction of ICG measured. Since the extraction ratio changed insignificantly with angiotensin (+0.04), changes in ICG clearance were judged to reflect changes in EHBF. Average control clearance of ICG was 404 ml/min/m² and fell by 16% ($P < 0.001$) with angiotensin. The changes in ICG clearance were not significantly correlated with changes in MAP, diastolic pressure, systemic resistance, or cardiac output. Responses to angiotensin were similar in the normal, hypertensive, and cardiac groups. In five patients so studied, splanchnic oxygen consumption was not significantly changed by angiotensin. It is concluded that angiotensin in these doses significantly decreases the clearance of ICG and hepatic blood flow independent of alterations in cardiac output, heart rate, diastolic pressure, or MAP.

Reversible Cor Pulmonale due to Hypertrophied Tonsils and Adenoids: Studies in Two Cases (P)

Jacqueline A. Noonan, Lexington, Kentucky

Two children, aged two and four years, presented with unexplained severe right-heart failure and somnolence. Each had marked cardiac enlargement and right ventricular hypertrophy. Both had tremendous tonsils and adenoids with snorting respirations and unbelievably severe upper airway obstruction while lying flat.

Cardiac catheterization studies indicated alveolar hypoventilation. A marked drop in vascular pressures with inspiratory efforts was consistent with upper airway obstruction. Studies of blood from the femoral artery revealed pO_2 of 54 and 37 mm Hg in the two patients and pCO_2 of 62 and 63 mm Hg. The pulmonary artery pressures were elevated to 55/28 mm Hg and 50/30 mm Hg. In one child a rise in pulmonary artery pressure to 93/65 mm Hg occurred during breathing of 100% oxygen. This unusual response was due to further carbon dioxide retention, the pCO_2 rising to more than 100 mm Hg. Uncompensated respiratory acidosis also resulted, with a fall in pH to 7.14. This patient illustrates well the hazard of oxygen administration to a patient with hypercapnia since correction of hypoxia may abolish the hypoxemic stimulus to ventilation, resulting, in turn, in further hypercapnia and severe respiratory acidosis.

Radiation therapy to the nasopharynx caused the lymphoid tissue to regress, and cardiopulmonary function subsequently returned to normal in both children. Cor pulmonale from hypertrophied tonsils and adenoids has not previously been reported but does seem to constitute a valid but rare medical indication for tonsillectomy and adenoidectomy.

Effects of Internal and External A-C and D-C Countershocks on Totally Implantable Pacemaker Function

John C. Norman and William J. Robinson, Boston, Massachusetts

The emergency treatment of ventricular tachycardia or fibrillation in patients with previously inserted implantable pacemakers may necessitate the use of external or internal defibrillators. The purpose of this study was to determine the effects of a-c and d-c defibrillators on pacemaker function in experimental animals.

Heart block was produced in a series of adult mongrel dogs. Standard AMPT-67 pacemakers without protective circuitry (Zener Diode) were inserted after initial recordings of each pacemaker's rate, stimulus waveform, and energy output per pulse. In open-chest preparations external and internal a-c and d-c countershocks were delivered from recommended minimal up through maximal defibrillatory output settings.

Acute and chronic redeterminations of each pacemaker's rate and individual stimulus characteristics revealed no changes from precountershock baselines, except in one instance in which the rate tripled, the type of waveform remained constant, and the energy per pulse decreased 75%. This change was induced with a single internal a-c countershock delivering 550 v for 150 msec.

The conclusions are that these types of implantable pacemakers can usually withstand a-c and d-c countershocks. However, postdefibrillation pacemaker-induced tachycardias or decreases in energy output per pulse below threshold, resulting in a loss of pacing, may occur and require further emergency measures.

Hemodynamic Effects of Nitroglycerin in Coronary Disease

Paul Novack, Douglas M. Griggs, Jr., Harris Forman, Hratch Kasparian, and Albert J. Kaspar, Philadelphia, Pennsylvania

In an effort to test the hypothesis that nitroglycerin diminishes cardiac oxygen requirements by reducing the mechanical work of the left ven-

tricle, 20 patients with coronary disease have been studied by right-heart catheterization at rest and during exercise prior to and following the sublingual administration of 0.1 mg nitroglycerin. The exercise response was characterized by left ventricular failure, as indicated by an abnormal rise in pulmonary artery pressure from 24/8 (14) to 48/23 (35) mm Hg. Although nitroglycerin resulted in a reduction of resting left stroke work from 62 to 46 g-m/beat/m^2 ($P < 0.001$), this was not significantly different during exercise, measuring 94 g-m/beat/m^2 during control exercise and 88 g-m/beat/m^2 during exercise after nitroglycerin. Pulmonary artery pressure, however, was significantly lower following nitroglycerin, both at rest, 17/5 (ten) mm Hg ($P < 0.001$), and during exercise, 36/14 (22) mm Hg ($P < 0.001$). Since, in the absence of pulmonary vascular disease, pulmonary artery diastolic pressure reflects left ventricular end-diastolic pressure and volume, these results suggest an improvement in left ventricular function following nitroglycerin. Such an effect could be due to increased coronary blood flow but more likely is due to peripheral pooling of blood, which leads to a heart of diminished radius that is thus capable of performing the same stroke work with a lesser oxygen requirement (Laplace effect).

Micropuncture Determination of the Potassium Absorption Profile in Rat Proximal Tubule Using Potassium-Sensitive Glass Electrodes (P)

Donald E. Oken, Boston, Massachusetts

The potassium concentration of rat proximal tubule fluid has been shown to be lower than that of plasma as the result of active transport processes. No significant decrease in potassium concentration beyond the first 20% of proximal tubule length could be shown statistically, perhaps because of the wide spread of data. If potassium does remain constant despite continued sodium absorption in the remainder of this tubule segment, a direct relationship between sodium and potassium transport must be envisaged. This study has attempted to test this relationship by means of potassium-sensitive glass microelectrodes inserted at progressively distal sites in single proximal tubules with micropuncture techniques.

Potassium concentration was assayed in 15 rats at three sites in each of three proximal tubules, at two sites in each of 11 tubules, while single values were obtained in 17 tubules. Mean potassium concentration of plasma and proximal tubule fluid samples were 4.4 ± 0.1 mEq/L (SE) and 3.0 ± 0.1 mEq/L, respectively. Mean tubule fluid to plasma potassium ratio was 0.69 ± 0.02, a value statistically less than 1.0 ($P < 0.001$). As in previous studies no statistically significant decrease in potassium concentration was found ($P < 0.1$) on pooling data from the various nephrons. When values obtained in each tubule were analyzed separately, however, potassium concentration was seen to be consistently and significantly lower at sites more distant from the glomerulus ($P < 0.001$). A seemingly direct interrelationship between active absorption of sodium and potassium in the proximal tubule of rat kidney is thereby excluded.

Transmembrane Potentials of Tissue-Cultured, Single Pacemaker Cells Before and After Cardiac Glycoside-Induced Fibrillation

Yoshiaki Omura and Brian F. Hoffman, New York, New York

Fibrillation was induced by a high concentration of digoxin (final concentration 1.2 to 1.6×10^{-6} M) in spontaneously beating, tissue-cultured cardiac pacemaker cells originally separated from embryonic chick heart. Before and after digoxin administration the transmembrane action potentials (TAP) were recorded continuously from two single pacemaker cells separated by about 200 μ in the same beating quasi-monolayer. When typical fibrillation of these cells was observed under a magnified inverted microscopic field, the transmembrane potential (TP) with a decreased absolute magnitude showed typical oscillatory sinusoidal waveforms, most of which, however, showed that the total time duration of the rising phase was almost the same as (particularly when amplitude was large) or longer than the total time duration of the falling phase. Fibrillatory movements of each part within the fibrillating, individual cardiac cells appeared to be synchronized with the sinusoidal waves of TP. Defibrillation with hyperpolarization and arrest of the cells was obtained within 15 seconds after administration of calcium gluconate (Ca-G) (final concentration 15 mg/100 ml medium). Further increase in the concentration of Ca-G did not produce any further changes. A fresh change of culture medium induced the arrested cardiac cells to contract regularly with an increased rate, accompanied by a corresponding, nearly normal TAP with a decreased threshold stimulation potential. Additional digoxin treatment not only induced fibrillation again in one part of the cell group surrounding one microelectrode, but also induced irregular, prefibrillatory contraction of the cell group around the other electrode located 200 μ from the first. However, this fibrillatory movement appeared without a corresponding change in TP, while irregular contractions were accompanied by corresponding irregular TP

changes. Repeating the same process with digoxin, Ca-G, and change of medium, we occasionally observed similar decoupling phenomena between electrical and mechanical activities.

Simultaneous studies of both TP and mechanical phenomena indicated the following: (1) When all the cells are typically fibrillating, the corresponding TP shows an oscillatory, sinusoidal waveform. (2) Within a less than 200-μ length of one cardiac cell mass, two cell groups with completely different mechanical and electrical activity can coexist. (3) In a series of repeated treatment of tissue-cultured, spontaneously beating cardiac cells, decoupling phenomena characterized by the existence of mechanical fibrillatory movement without any corresponding changes in transmembrane potential can occur.

Peritoneal Dialysis for Refractory Congestive Heart Failure

Gaddo Onesti, Charles H. Heider, William M. Lemmon, Charles D. Swartz, and Albert N. Brest, Philadelphia, Pennsylvania

Ten patients with congestive heart failure refractory to digitalis and diuretic therapy were subjected to peritoneal dialysis with hyperosmotic solutions. The average dialysis time was 36 hours. The average weight loss per patient was 15 lb., and the average excess peritoneal fluid removed was 9 L per patient. Blood volume determined by RISA decreased an average of 1,300 ml per patient. This decline was 24% of predialysis volume; 80% of the contraction in blood volume occurred in the plasma compartment. The venous pressure decreased an average of 90 mm H_2O per patient, and circulation time decreased an average of nine seconds per patient.

Cardiac output determined by dye-dilution in five patients before and after dialysis showed no significant change. Likewise, there were no significant alterations in intra-arterial pressure, renal blood flow (PAH clearance), or glomerular filtration rate (inulin clearance).

All patients demonstrated marked clinical improvement. Three patients had severe hyponatremia corrected by dialysis. There were no adverse reactions to peritoneal dialysis in these ten patients.

Peritoneal dialysis is a safe, effective method for controlling fluid retention in patients with refractory congestive failure who do not respond to maximum anticongestive drug regimens. In addition, electrolyte normality is restored by this procedure. However, it is noteworthy that no significant increase in cardiac output or renal function was obtained in this group of patients.

Initiation of Oral Anticoagulation by a New Low-Dose Method

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The conventional initiation of oral anticoagulation (initial loading dose of drug followed by progressively smaller doses until a maintenance level is reached) has the undesirable features of dose variability and the possible danger of excessive anticoagulation. The coumarin anticoagulant, warfarin, has been used in normal subjects and cardiac patients to compare the prothrombinopenic response of a new method of low, constant daily doses (10 or 15 mg) with that of the large loading dose method. The parameters serially followed were blood levels of warfarin, prothrombin time, and clotting factors II, VII, IX, and X.

A ceiling for the speed of prothrombinopenia exists since single warfarin doses up to 800 mg did not cause a faster onset than 50 mg. The time required to achieve less than 35% prothrombin activity was 1.1 days with the large doses, 2.2 days with 15 mg a day, and 4.7 days with 10 mg a day. The more rapid onset of therapeutic prothrombinopenia was due solely to a faster fall in factor VII since those factors involved with intravascular coagulation (II, IX, and X) fell just as rapidly with the 15-mg daily dose as when large loading doses were used. The maintenance dose of warfarin and its level in the subject's blood were nearly identical whether therapy was initiated with a large loading dose or a small, constant one. Small, constant doses should be the regimen of choice for initiating oral anticoagulation.

Unusual Observations in Supravalvular Aortic Stenosis (P)

Harry L. Page, Jr., John H. K. Vogel,‡ Ray Pryor, and S. Gilbert Blount, Jr., Denver, Colorado

Since the renewal of interest in supravalvular aortic stenosis by Denie and Verheught in 1958, the clinical and genetic characteristics of this lesion have been better defined. Two distinct patient groups have been described. As an isolated lesion in mentally normal patients, a familial occurrence has been frequently observed. Occurring sporadically, it has been described in association with mental deficiency, a peculiar facies, unusual dentition, and peripheral pulmonary artery stenosis and possibly represents the late sequelae of spontaneously resolved severe infantile hypercalcemia. It is the purpose of this paper to present

from our experience certain unusual and previously unreported features of this problem.

Twelve-year-old, mentally deficient, identical male twins were found to have evidence of supravalvular aortic stenosis and multiple peripheral pulmonary artery stenoses. These twins have the characteristic facies originally described by Williams and represent the first reported familial incidence of the more extensive syndrome. The finding of a ventricular septal defect in one of these twins likewise constitutes a unique observation.

A 37-year-old mentally deficient male with typical facies and supravalvular lesion died with a *Streptococcus viridans* endarteritis originating in a plaque above the stenosis. At postmortem examination the mitral valve annulus was extensively calcified without evidence of congenital or rheumatic deformity of the valve leaflets. The possible relationship of this calcification to unrecognized infantile hypercalcemia, the unprecedented age of this mentally defective patient, and the terminal episode of endarteritis also represent new additions to the natural history of supravalvular aortic stenosis.

Specific Immunochemical Method for Quantitative Determination of Angiotensin (P)

Lot B. Page, Edgar Haber, and Saima Lagg, Boston, Massachusetts

All currently available methods for angiotensin determination are based on bioassay. These methods are cumbersome and lacking in specificity, and their use has yielded conflicting results.

Angiotensin was rendered antigenic by coupling it covalently to poly-L-lysine to form compounds of 20,000 to 30,000 molecular weight. Two types of copolymers were synthesized, differing in the orientation of the angiotensin molecules with respect to the poly-L-lysine backbone.

Both compounds elicited production of antibody specific for angiotensin in rabbits. Binding of isotope-labeled angiotensin to antibody was demonstrated by means of gel filtration. Reproducible displacement of angiotensin-I^{125} by unlabeled angiotensin forms the basis of quantitative immunoassay. In buffer systems, as little as 25 $\mu\mu$g of angiotensin was detected. Unlabeled angiotensin added to human plasma could be detected at a concentration of 100 $\mu\mu$g per ml. The method appears to be completely specific for angiotensin, even in the presence of large excesses of other polypeptides.

Preliminary data suggest that immunochemical methods may be able to distinguish between angiotensin II and its decapeptide precursor (angiotensin I), allowing separate quantitative determination of each polypeptide.

Quantitative immunochemical determination of angiotensin has a wide area of application in human physiology, clinical disease states, and experimental models.

Effect of Beta-Adrenergic Receptor Suppression on Left Ventricular Response to Exercise in Man (P)

Hyman W. Paley, Ian G. McDonald, and Frances W. Peters, San Francisco, California

Propranolol, a beta-adrenergic receptor suppressant, has been used to study the mechanism of left ventricular (LV) adaptation to exercise in normal man. Six supine subjects were studied at rest and during exercise (75 w) under control conditions and within 20 minutes after intravenous administration of 15 mg of propranolol. Cardiac output (indicator-dilution), LV volume (thermodilution), heart rate, arterial blood pressure, and LV ejection time were determined. It was assumed that the LV behaves as a contracting sphere, and mean rate of circumferential shortening (MRCS) and mean force during ejection (F_{me}) were calculated. There was no significant difference between F_{me} during exercise alone or following propranolol at rest and control resting values. F_{me} was only slightly increased during exercise following propranolol, mainly because of an increase of LV end-diastolic volume which was not observed in other conditions of this study. However, MRCS increased 64% (14.6 to 23.9 cm/sec) during exercise alone, while this index of velocity of contraction increased only 14% (14.6 to 16.6 cm/sec) under the same condition following propranolol. Propranolol at rest diminished MRCS slightly but significantly when compared with control resting values. This indication of force-velocity relationships within the LV wall demonstrates that propranolol suppresses the positive inotropic response to exercise and suggests that it reduces myocardial contractility at rest. Compared to more conventional indications of LV performance, the F_{me}-MRCS relationship more clearly demonstrates the effect of propranolol. When correction was made for alleged discrepancies of LV size determined by thermodilution and compared with radiographic methods, there was no essential difference from the conclusions drawn above.

Percutaneous Approach to Left and Right Intracardiac Sounds

Carlo A. Pallini, Russel W. Brancato, Leonard Weinstein, Danelo R. Canete, and Nicholas A. Antonius, Newark, New Jersey

An intracardiac phonocatheter which permits the registration of sounds from all left- and right-

heart chambers by the percutaneous route has been developed. It consists of a subminiature, polarized, piezoelectric ceramic element in a sealed Teflon tube, 0.040 inch in diameter. Its acoustical characteristics are satisfactory, and it is autoclavable.

The technique of use consists in advancing a no. 7 French Teflon catheter into the heart by the percutaneous puncture of a peripheral vein or artery and by gaining access to the left atrium transseptally. The sound probe is then introduced into the catheter and advanced to the tip, where sounds are recorded. Pressures can be simultaneously obtained via the housing catheter since the sound probe does not occlude its lumen completely. This phonocatheter can therefore be positioned and intracardiac sounds recorded in any location in the cardiovascular system without excessive manipulation and time loss. Accordingly, intracardiac sounds have been obtained in the left atrium, left ventricle, and aorta of over 100 patients.

The findings included the following: In combined mitral valve disease murmurs are loudest in the left ventricle, whereas sounds are loudest in the left atrium. In aortic valvular disease systolic and diastolic murmurs are seen both in the aorta and the left ventricle. Occasionally, an aortic regurgitant murmur may appear in the right ventricle as well. Aortic insufficiency has not been found in the absence of a left ventricular diastolic murmur. Loud systolic murmurs of uncomplicated ventricular septal defects may be seen in both ventricles.

Tricuspid and Mitral Insufficiency in Normal Dogs

Brent M. Parker, Howard L. Hudson, Robert M. Smith, St. Louis, Missouri, and Marvin J. Friedenberg, Palm Springs, California

Reflux has been observed through apparently normal valves during angiocardiography. However, studies on relative mitral insufficiency are conflicting, and tricuspid insufficiency has received scant attention. This report details the incidence and mechanisms of mitral and tricuspid insufficiency in 107 injections in 36 normal dogs.

Fifty-three right ventricular and 54 left ventricular injections were made. For the right ventricular studies, the catheter was passed either through the tricuspid valve or retrograde through the pulmonic valve and, in the left ventricular studies, through the aortic valve.

The following conditions were varied: Injection pressure (300 or 800 psi), catheter size (no. 8 or 11 French), and volume of contrast agent (1.0 or 1.5 ml/kg). The electrocardiograph was monitored, and both cineradiography and serial filming were utilized.

Valvular insufficiency was observed in 80% of the injections (86 of 107). The frequency of mitral and tricuspid insufficiency was equal. Although insufficiency was major in a few injections (19 of 107), most showed a small puff of reflux which cleared quickly. Insufficiency occurred primarily during ventricular systole and was often associated with a ventricular premature contraction. Associated with greater amounts of insufficiency were (1) arrhythmia, (2) catheter through the valve, (3) high injection pressure, (4) large catheter size, and (5) larger amounts of contrast agent.

In clinical angiocardiography one should interpret small amounts of reflux cautiously when the catheter passes through the valve, when arrhythmia is present during injection, or when large catheters and large amounts of contrast agent are used.

New Experimental Model for Intracardiac Cinematography (P)

Luke R. Pascale, Chicago Heights, Illinois, Ara V. Dumanian, East Chicago, Indiana, Henry G. Giragos, and Richard J. Wallyn, Chicago Heights, Illinois

A method for intracardiac endoscopy was established to study the internal mechanics of the heart. Healthy mongrel dogs were anesthetized and placed on 100% oxygen through a cuffed endotracheal tube in a hyperbaric chamber. The abdominal aorta was cannulated for bleeding, and the inferior vena cava and left jugular vein were cannulated for infusion. The right jugular vein was prepared to receive a Carlens-Silander cardioscope. Arterial pressure, electrocardiograms, and electroencephalograms were monitored. The hyperbaric chamber was pressurized to 45 psi gauge pressure, and the exchange infusion was begun. The perfusate consisted of a solution which was isotonic for Na, K, Ca, Mg, Cl, HCO_3, plus THAM (tris [hydroxymethyl] aminomethane), low molecular weight dextran, and glucose. The fluid, warmed to 33 C, was infused at the rate of 500 ml/min. The cardioscope was introduced into the right side of the heart via the right jugular vein. The aortic cannula drainage became free of apparent red blood cell components except for a slight yellow tinge after 32 to 50 L of fluid had been exchanged. A clear view of the interior of the right atrium and ventricle was obtained. Black and white and color cinephotographs were taken, using an 8-mm Leicina camera adapted to the eyepiece of the cardioscope. The constricting action of the annulus of the tricuspid valve, the closure of the valve leaflets, the contraction of the papillary muscles, and tensing of the chordae tendineae could be seen.

Longitudinal Tethering of the Aorta

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It is generally recognized that the motion of a blood vessel in longitudinal direction is restricted by tethering of the surrounding tissues. Direct measurements of these tethering forces have been lacking. Under certain restricted conditions the dynamic behavior of the vascular system becomes very sensitive to the magnitude and nature of these tethering forces. Therefore, it is important to quantify vascular tethering to determine its proper role in circulatory physiology. The relationship between longitudinal vessel motions and associated tethering forces was studied at three sites along the aorta in 20 dogs immediately postmortem. The vessel segment of interest was fitted and tightly coupled in situ to a cylindrical plastic plug. The distal and proximal vessel was then severed to isolate the segment of interest. Longitudinal displacements were applied to the plug and its captured sleeve of tethered vessel. Forces and displacements were measured continuously with specially designed transducers. By means of analogue and digital computer techniques, the data were analyzed with various linear models. A model consisting of vascular mass coupled to both series and parallel combinations of elastic and frictional elements was found most consistent with experimental observations which were as follows: (1) a damped sinusoidal transient response superimposed on an exponential creep; (2) a mechanical impedance that increased initially, then decreased to a minimum value, and then increased thereafter with frequency; and (3) an elastic tethering constant (k, the ratio of force to displacement), which was surprisingly linear and increased with distance along the aorta.

Adjunctive Use of a Surface-Active Agent in Extracorporeal Circulation (P)

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Theoretical considerations indicate that surface-active agents might protect the red cell from damage during prolonged extracorporeal circulation and reduce protein denaturation, hemolysis, and fat embolism. The nonionic detergent polyoxyethylene glycol (Pluronic F68) was selected for study.

Disposable bubble oxygenators were used to perfuse 40 dogs for two hours. In 20 experiments the perfusates were dextrose in water, dextrose in saline, Ringer's solution, and whole blood. Twenty additional dogs were perfused with dextrose in 0.2% saline for two, three, or four hours: polyoxyethylene was added to the perfusate to equal 0.6 mg/ml perfusate (blood volume plus prime). All dogs were studied for changes in electrolytes, acid-base, plasma hemoglobin, and urinary output; dogs in each group were sacrificed for histological examination for fat emboli.

Ninety-five per cent of the dogs survived the perfusions: all unsacrificed polyoxyethylene treated dogs survived (seven, after three-hour perfusions; one, after four-hour perfusion). There were no differences in blood or oxygen flow rates, acid-base balance, or urinary output in any group.

Plasma hemoglobin levels after two hours ranged between 110 mg% in dogs perfused with 5% dextrose in water to 44 mg% after perfusion with Ringer's. After three hours perfusion with polyoxyethylene, the plasma hemoglobin never exceeded 35 mg%. Histological evidence of fat embolism was found in four of six dogs perfused without polyoxyethylene but was not found in any of six dogs given F68.

Blood losses were not increased by the addition of polyoxyethylene, and in vitro coagulation studies did not reveal alterations in clotting.

Evaluation of the Intracardiac Bipolar Catheter Pacemaker in the Management of Complete Heart Block Developing as a Complication of Acute Myocardial Infarction (P)

E. Alan Paulk, Jr., and J. Willis Hurst, Atlanta, Georgia

The development of complete heart block (CHB) represents a grave complication in patients with acute myocardial infarction (AMI), and medical therapy has not been satisfactory. A prospective study was designed to evaluate the use of the bipolar electrode catheter (BEC) in those patients who developed CHB during the course of AMI. In approximately 1,400 admissions for AMI, 47 patients (3.3%) were recognized as developing CHB. There were 41 patients (the study group) in whom a BEC was inserted.

Nineteen patients died during the hospitalization. Twelve of the 19 patients had cardiac arrest requiring resuscitation (CA-R), and 14 were in shock prior to the time of insertion of the BEC. Five patients died from rupture of the left ventricle, three from irreversible shock, two from ventricular fibrillation, and two from asystole. Seven deaths were from miscellaneous causes.

Of the 22 patients who survived, seven had CA-R, and 11 had shock prior to the time of pacemaker insertion. Normal sinus rhythm was re-established in 17 of the 22 survivors, and CHB persisted in only five. Three of these five patients later required an implanted pacemaker.

Thirty-two out of 41 patients had either syncope or CA-R before catheter insertion. Nineteen

of the 41 patients in the study group had CA-R before BEC insertion, and in this group the mortality rate was 63%. Twenty-two patients developing CHB, but without major cardiac arrest, had a mortality rate of 31%.

Salvage of Limbs by Arterial Reconstruction: Improved Results by Extended Criteria of Operability (P)

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Advanced arterial occlusive disease associated with gangrenous change or chronic pain at rest necessitates major amputation of the lower limb. Salvage of the limb has been achieved by arterial reconstruction, which may improve circulation and thus relieve pain or permit healing after digital or transmetatarsal amputation. The number of patients benefited by arterial bypass or endarterectomy has been limited in most centers, however, by (1) confinement of operation to patients with reasonably normal arterial outflow distal to the occlusive process and (2) hesitation to submit the patients, often afflicted with cardiopulmonary or renal disease, to major operations.

In an effort to increase salvage of limbs, a decision was made in 1964 to attempt arterial reconstruction in every patient with a detectable patent arterial segment, however small, distal to an occlusive lesion. During the preceding six years, about 85 major amputations, above or below knee, were performed each year; during the year since institution of the policy, only 41 major amputations have been performed, whereas the number of operations for arterial reconstruction has more than tripled that during any previous 12 months. Simultaneously, the number of digital and transmetatarsal amputations has increased considerably. During the past year the fatality rate for aortoiliac reconstruction has remained about 5% and that for femoropopliteal reconstruction about 3%. These results are particularly significant because of the relatively consistent racial and economic population and total number of admissions at Charity Hospital during the past seven years.

Serum Lactic Dehydrogenase Isozymes with Embolization of the Dog Limb

Raymond Penneys, Barry Goldberg, Vincent J. Cristofalo, George Gauthier, and Bryan S. Johnson, Philadelphia, Pennsylvania

The lactic dehydrogenase (LDH) isozyme of skeletal muscle contains cathodal bands so that its detection in the serum should indicate breakdown of skeletal muscle. The development of a rapid and practicable microelectrophoretic method by Wieme and Blanchaer led to an investigation of the possible appearance of this isozyme in the serum of animals with severe ischemia of muscle.

The hindlimb of 20 dogs was embolized by the infusion of lycopodium spores into the femoral artery; blood samples were taken from the systemic circulation 24 to 72 hours later. Results were as follows: (1) Intense cathodal bands were always present in the serum if the electrophoresis apparatus was cooled with ether; (2) these bands remained essentially unchanged in serum samples stored at −20 C for over three weeks; (3) hemolysis of blood samples had to be avoided since the LDH of dog red blood cells may contain cathodal bands.

Serum LDH isozymes should be of value, therefore, in the study of the severely ischemic limb since they provide a much needed index of damage to the skeletal muscle.

Functional Regional Circulation in the Myocardium of Pig and Dog Determined by Rb^{86} Uptake and I^{131}-Albumin

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Nutritional circulation and blood content of various regions of the heart of dogs and pigs were compared. Rb^{86} uptake by the myocardium occurs in functional capillaries and, therefore, is related to the nutritional blood flow. I^{131}-albumin remains essentially within the vascular compartment and was used to approximate the blood content. Under anesthesia the isotopes were injected intravenously, and the heart was fibrillated ten minutes later. The heart was unrolled and sections taken from both atria, the right (RV) and left ventricles (LV), the intraventricular septum (IVS), and papillary muscle (PM). A sample of skeletal muscle was also removed. In the pig RB^{86} uptake (count/min/100 g) did not vary significantly among the various sections of the heart, but in the dog the left ventricular sections (LV, IVS, and PM) showed higher values than the atria or RV. The ratio of LV to RV Rb^{86} uptake was 1.1 for pig and 1.9 for dog. These data compare with the gross anatomical variations of coronary blood supply in pig and dog. The blood content /100 g of tissue in the pig was the same in all sections of the heart. The heart accumulated 20 times as much Rb^{86}/100 g as skeletal muscle, even though the blood content was only four times greater.

Effects of Hyperbaric Oxygenation on Acute Myocardial Infarction in Pigs (P)

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This study was designed to evaluate further the possibly protective effect of hyperbaric oxygenation (OHP) in experimental myocardial infarction caused by gradual occlusion of a coronary artery in the pig. This animal was selected because of the similarity of its coronary circulation to that of man. Ameroid constrictors designed to produce complete closure within 48 hours were placed on the left anterior descending coronary artery of 24 pigs weighing 25 to 35 lb. Sixteen hours after constrictor placement, when the pigs were ambulatory, they were randomly divided into two groups. Twelve pigs, group A, were placed in a hyperbaric chamber large enough to permit freedom of movement at 1.25 atmospheres absolute while breathing 100% O_2 for a maximum of 32 hours. Twelve pigs, group B, were handled similarly outside the chamber while breathing air at normal atmospheric pressure. Group A pigs lived 24 to 72 hours after surgery (mean 46.8 hours), group B pigs lived 16.5 to 31 hours (mean 21.6 hours). Death occurred in both groups suddenly and unexpectedly. Telemetered electrocardiograms demonstrated that the sudden death was due to ventricular fibrillation developing after progressive ST-T segment depression. Pathological and histochemical studies of the hearts revealed striking differences between the two groups. Nine pigs in group A (OHP) had significant myocardial infarctions, whereas only two pigs in group B (control) showed any evidence of infarction. These findings suggest that modest but prolonged OHP may protect the pig from ventricular fibrillation for a sufficient period of time to allow him to develop a pathologically detectable myocardial infarction.

Diagnosis of Tricuspid Insufficiency from Flow Velocity Changes Within the Central Circulation

Arthur O. Phinney, Jr., Peter V. Stoughton, and Charles E. McLean, Hartford, Connecticut

A majority of chronically ill patients who succumb following mitral open-heart surgery have marked cardiomegaly and right-heart failure, augmented by unsuspected tricuspid insufficiency (TI). The need for better preoperative TI evaluation has been further emphasized by the availability of newer, corrective, right-sided approach techniques such as ball valve replacement. By means of selective injections of Coomassie Blue dye into pulmonary artery (PA), right ventricular inflow (RVif), and right atrial inflow (RAif) tracts, earpiece dye curves have recorded an orderly increase in appearance time (AT), predictably, in 30 patients without significant hemodynamic lesions. By contrast, in six patients with massive TI indicated at operation or autopsy, a derangement was noted in the successive AT delay as the injection site was moved upstream, together with a diagnostic change in dye curve pattern recorded from RV and RA injections. The AT from RA injection, frequently equal to or shorter than that from RV, illustrated the increased velocity of diastolic flow across the incompetent segment, or tricuspid valve. Arrival of dye particles in the physiological stream through a multiperforate catheter was measured precisely by an electronic injection timer.

All six patients had apical systolic murmurs and marked dilatation of RA and RV, and the diagnosis of TI was questioned clinically. However, although mean RA pressures were 8 mm Hg or more in all patients, only one had an RA pulse tracing suggestive of TI. Demonstration of the flow characteristics of the systemic circulation appeared to yield the only hemodynamic diagnostic clue to the presence of this subtle lesion.

Valve Replacement: Durability of Silicone Rubber (P)

Will Pierie, Don Raible, George Siposs, M. Lowell Edwards, Santa Ana, California, and Albert Starr, Portland, Oregon

Accelerated fatigue tests and clinical experience have demonstrated the remarkable durability of silicone rubber as used in spherical form in the mitral ball-valve prosthesis. Attention is directed here to an evaluation of this material in the aortic prosthesis.

From 1962 to May 1, 1965, 10,454 aortic prostheses have been sold by the manufacturer, and 860 aortic valves have been returned for reprocessing. Balls obtained from autopsy material can be traced through their serial number, and their size, weight, shape, and Shore hardness can be compared with measurements made at the time of manufacture. Seven balls have shown evidence of injury with some or all of the following abnormalities: (1) loss or gain in mass, (2) change in color, consistency, and shape, and (3) compression set from cage struts or valve seat. In two instances death was related to ball dislocation.

Accelerated fatigue tests of silicone rubber balls were performed with variations in (1) Shore hardness, (2) opening and closing pressures, (3) valve design, (4) restriction of trajectory, and other parameters. Ball abnormalities could

be reproduced in part under some of the test circumstances.

It is concluded that malposition of the prosthesis or mechanical damage to the highly polished contact surfaces may predispose to ball injury. Small changes in valve configuration and the curing process of silicone rubber may influence the margin of safety on accelerated fatigue testing. The possible role of chemical deterioration requires further study.

Correlation of Vectorcardiographic Criteria for Myocardial Infarction with Autopsy Findings (P)

Raymond J. Pietras, Jorge Blackaller, Chicago, Illinois, Stewart Dadmun, San Diego, California, John R. Tobin, Jr., and Rolf M. Gunnar, Chicago, Illinois

A total of 108 patients who had scalar electrocardiograms and vectorcardiograms (Frank corrected lead system) were followed to autopsy. Their hearts were carefully dissected by lamination, and areas of infarction, if present, were mapped. Vectorcardiograms were analyzed according to previously established criteria for the diagnosis of myocardial infarction. Scalar electrocardiograms were read by two observers independently. Fifty-three hearts contained significant areas of infarction. Vectorcardiograms predicted the areas of myocardial infarction correctly in 40 hearts, and scalar electrocardiograms predicted the areas of infarction correctly in 22 and 23 hearts (as interpreted by the two observers). Myocardial infarction was predicted by vectorcardiography but was incorrectly localized in six hearts and by electrocardiography in six and five hearts. In seven hearts there were significant areas of myocardial infarction not predicted by vectorcardiography, and this occurred in 25 hearts analyzed by scalar electrocardiography. In 12 hearts the vectorcardiogram indicated myocardial infarction when no significant infarct was found at autopsy, and this occurred in 18 and 17 hearts analyzed by scalar electrocardiography.

The vectorcardiogram commonly failed to detect myocardial infarction when infarcted areas were small and disclosed only terminal conduction delay or when associated with severe mitral stenosis or right bundle-branch block. The vectorcardiogram falsely indicated myocardial infarction when dissection and histology disclosed severe left ventricular fibrosis, severe left ventricular hypertrophy, and myocardial amyloidosis.

In this series the vectorcardiogram had a distinct advantage over the standard scalar electrocardiogram in the diagnosis of myocardial infarction.

Limitations on the Equivalent Cardiac Generator

Robert Plonsey, Cleveland, Ohio

It is noted that electrocardiographic measurements are capable of determining the multipole expansion of the heart sources. The presence of noise will limit the maximum multipole that is capable of detection to a finite value N. It is necessary, therefore, that a correct physical model, such as a fixed dipole, double layer, moving dipole, or multiple dipole, etc., must be capable of reproducing the multipole expansion up to and including the Nth multipole. However, an infinite number of such sources, covering an extremely wide range of distributions, will be capable of yielding the same multipole expansion (to the Nth terms) and, hence, will be consistent with the same electrocardiographic data. Consequently, any specific solution to the moving dipole or multiple dipole model will, in general, be unrelated to the true source distribution, and those models are invalid. Other models which make *a priori* assumptions concerning distributions or inhomogeneities must similarly be discarded for lack of uniqueness in the inverse problem. The multipole expansion itself is all that can be obtained from electrocardiographic measurement.

Accordingly, the present problem facing investigators of the inverse problem in electrocardiography is (1) to determine how many multipole terms can, as a practical matter, be detected and (2) to find an optimum lead system for such determination that can be utilized clinically and that yields reproducible data.

Relationship Between Cardiac Output and Renal Function in Valve Replacement Surgery: Role of Mannitol

George A. Porter, Frank E. Kloster, Albert Starr, and Herbert E. Griswold, Portland, Oregon

Simultaneous measurements of cardiac output and creatinine and osmolar clearance were performed in 14 patients before, during, and at intervals for three weeks after prosthetic valve replacement. The mean creatinine clearance during bypass, corrected for cardiac output, was 50% greater in mitral valve replacement than in aortic valve replacement and 130% greater than double valve replacement. Plotted against duration of bypass, these data yielded a significant negative correlation ($r = -0.72$). Recovery of renal function during the postoperative period paralleled improvement in cardiac output in the three groups.

In 13 additional valve replacement patients the duration of cardiopulmonary bypass was eliminat-

ed as a variable by comparing sequential 30-minute clearance periods. Spuriously high creatinine clearance occurred during the first 30 minutes regardless of the valve replaced, presumably due to the "flushing effect" of the mannitol diuresis. These findings, coupled with the shorter time of bypass during mitral replacement, probably explain the group differences noted above. From 30 to 120 minutes of bypass, creatinine clearance declined from 70 to 39 ml/min/1.73 m^2, while PAH clearance remained stable. The decline in creatinine clearance was independent of changes in cardiac output and occurred despite a sustained mannitol diuresis. Renal concentrating capacity was not impaired by osmotic diuresis since all patients achieved a U/P osmolar ratio greater than 2.5 18 hours after surgery.

Although mannitol diuresis during cardiopulmonary bypass may sustain renal plasma flow, as judged by PAH clearance, it does not correlate with glomerular filtration rate. These findings are compatible with a redistribution of intrarenal blood flow.

Treatment of Endocarditis Due to *Pseudomonas aeruginosa* Following Cardiac Surgery

Robert S. Pressman, Dryden P. Morse, and Harry Goldberg, Philadelphia, Pennsylvania

Bacterial endocarditis occurs in approximately 1% of all cases after cardiac surgery but has been reported to occur as frequently as 20%. It appears to be encountered more often following exposure of the patient to a cardiopulmonary bypass technique. We believe that without an antibiotic "umbrella" during and after the period of surgery, endocarditis would be encountered with even greater frequency. Since the introduction of the so-called "synthetic penicillins," there has been an increasing number of reports of endocarditis due to unusual organisms. One of the most troublesome has been the *Pseudomonas* group. These microorganisms have proven amazingly resistant to the usual spectrum of known antimicrobial agents. By the middle of 1964, there were only six authenticated reports of cure of *Ps. aeruginosa* endocarditis. Several of these involved curing the patient by reoperating to remove infected sutures or prostheses. By using a combination of Cephalothin and polymyxin B, a new and successful nonoperative treatment of *Ps. aeruginosa* endocarditis has been devised. To date, three patients have been successfully treated with these two antibiotics in combination. The results of tube dilution studies indicate a synergism between Cephalothin and polymyxin B.

Myocardial Threshold and Impedance in Complete Heart Block: Methods for Assessing Pacemaker Function and Malfunction (P)

Thomas A. Preston, Richard D. Judge, Ann Arbor, Michigan, David L. Bowers, Milwaukee, Wisconsin, and Joe D. Morris, Ann Arbor, Michigan

Analysis of 120 pacemaker implants disclosed that the major causes for failure were (1) lead fracture, (2) battery failure, and (3) exit block. Fortunately, component failure has not been a problem. This experience emphasized the need for developing indirect methods of monitoring myocardial threshold and impedance to aid in identifying malfunction precisely and anticipating failure before they manifested themselves clinically.

The circuit design of one unit (General Electric Internal Pacemaker) has made possible the development of a simple and safe method of determining (1) threshold, (2) myocardial resistance, (3) electrode capacitance, and (4) battery level. All parameter measurements are made externally (without surgery) by analyzing various electromagnetic signals emitted by the pacemaker. Preliminary studies in dogs have shown the following: the methods are safe, it is possible to predict energy values from pulse signal analysis, and increases in rate cause increases in threshold. As expected, threshold proved to be a function of total pulse energy. With calibrated pacemakers it was possible to follow myocardial resistance and electrode capacitance after human implantation. In a series of 20 patients, capacitance varied insignificantly, while resistance increased gradually during the immediate postoperative period and then became stable. Myocardial impedance did not always vary directly with threshold changes. These studies not only demonstrate a simple, practical method of monitoring pacemaker function, but also promise a means of studying the electrophysiological effects of cardiac drugs in the future.

Selective Coronary Cinearteriography in Angina Pectoris and Myocardial Infarction: Distribution of Obstructive Lesions (P)

William L. Proudfit, Earl K. Shirey, and F. Mason Sones, Jr., Cleveland, Ohio

In a series of 1,000 unselected patients who had selective coronary cinearteriograms, 192 had severe obstruction (50% luminal narrowing of one or more major vessels) associated with a clinical diagnosis of angina pectoris on exertion; 76% (147) had at least 90% obstruction, and in 58% (111) the block was complete. Similar findings were encountered in 146 additional patients who had pain at rest as well as on exertion and in 86 cases

with electrocardiographic diagnosis of myocardial infarction without angina pectoris. More than 90% obstruction was found in 88% (76 of 86) of cases of angina pectoris of any severity with myocardial infarction, and in 65% the obstruction was complete.

In the whole group of 627 significantly abnormal arteriograms, the anterior descending artery was affected more frequently than the right, but complete obstruction was more common in the right. Involvement of multiple vessels was usual, although severe obstruction affected only a single vessel in 23% (76 of 338) of patients who had angina and 34% (58 of 172) of cases of myocardial infarction.

The electrocardiogram was normal in 78 patients who had exertional angina; 69% (54) had at least 90% obstruction of one or more vessels, and in 45% (35) the obstruction was total. When the electrocardiogram was abnormal but not suggestive of infarction, the percentages were 79 (46 of 58) and 64 (37 of 58), respectively. Patients who had myocardial infarction as well as angina on exertion but not at rest had percentages of 87 (40 of 46) and 63 (29 of 46), respectively.

Epinephrine-Induced, Early, Prenecrotic Disturbances of Myocardial Potassium, Glycogen, and Phosphorylase

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A decline or complete loss of the histochemically demonstrable potassium (modified method of Poppen et al.) in some areas of the rat's myocardium occurs as early as 10 to 15 minutes after subcutaneous injection of epinephrine (450 μg/100 g body weight), i.e., long before structural changes can be demonstrated by routine staining techniques. The potassium-depleted foci also show a decline of glycogen and of phosphorylase activity. They are spotty and located mainly in the subendocardium and apex where necrotic lesions usually ensue. Oxidative enzymes (succinic, lactic, and malic dehydrogenases, cytochrome oxidase) remain normal or are even somewhat elevated in the potassium, etc.-depleted areas. Sensitization with fluorocortisole (250 μg/100 g body wt subcutaneously during five days) greatly enhances the susceptibility of the heart muscle, so that a half-dose of epinephrine becomes extremely potent in producing the alterations mentioned. Analogous changes follow coronary artery ligature but do not occur after injection of other potentially cardiotoxic compounds (plamocid, dihydrotachysterol). An early, spotty depletion of potassium was also confirmed in samples taken from subendocardial versus subepicardial regions of the cat's heart muscle following injection of epinephrine. It is concluded that the simultaneously occurring, histochemically demonstrable changes in myocardial potassium and glycogen content and phosphorylase activity are sensitive and early indices of the onset and extent of (presumably hypoxic) damage inflicted by epinephrine on myocardial tissue.

The Precordial Honk

Charles E. Rackley, Robert E. Whalen, Walter L. Floyd, and Edward S. Orgain, Durham, North Carolina

Seven patients with an intermittent loud noise over the precordium have been studied to evaluate the presence and severity of underlying heart disease. Because this sound suggests the honking noise made by a goose, we elected to call it a "precordial honk." The precordial honk is a loud, high-pitched, often intermittent, vibrating noise occurring during systole. Six females and one male had routine cardiac studies which included electrocardiogram, chest X-rays, and phonocardiograms. All seven patients had complete right- and left-heart catheterizations including appropriate indicator-dilution curves, and six patients had cineangiocardiograms with injection of contrast material into the left ventricle. These studies indicated that the precordial honk could occur in three situations. Three patients had no detectable heart disease at the time of the study. One patient had unsuspected mitral insufficiency demonstrated at catheterization. The remaining three patients had known heart disease; two had rheumatic heart disease with severe mitral stenosis, and the third had suspected idiopathic myocardial hypertrophy with massive mitral insufficiency. The intermittent nature of the precordial honk, its wide variation in intensity associated with respiration and changes in body position, and its presence in subjects with no detectable heart disease suggest that the precordial honk is probably an extracardiac sound. It remains possible that small, intermittent amounts of mitral insufficiency may generate such sounds. However, mitral insufficiency was encountered in only two patients. Mitral insufficiency was not demonstrated by cardiac catheterization in three patients nor during mitral valve surgery in two patients.

Isolated Hypoplasia of the Right Ventricle and Tricuspid Valve

Gunay Raghib, Kenneth L. Jue, Paul Adams, Jr., Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

Isolated hypoplasia of the right ventricle and tricuspid valve is a rare congenital cardiac mal-

formation. Frequently, this malformation gives rise to a clinical picture similar to those of tricuspid atresia, severe pulmonary stenosis or atresia with intact ventricular septum, Ebstein's malformation, and congenital tricuspid stenosis. Correct clinical diagnosis is essential because of the possibility of definitive surgery in some cases of congenital tricuspid stenosis, severe pulmonary stenosis or atresia, and Ebstein's malformation.

Recently, two infants with this cardiac malformation were observed. One of these infants died at the age of three months; the other one is two months old and alive. The clinical picture in both infants was the same: there was cyanosis at birth, absent murmur, and respiratory distress. Roentgenograms showed slight cardiomegaly, right atrial enlargement, and slightly decreased pulmonary vasculature. The electrocardiograms were interpreted as showing right atrial enlargement, left ventricular hypertrophy, and poorly functioning right ventricle. The data of cardiac catheterization revealed elevated right atrial pressure and right ventricular end-diastolic pressure. The right ventricular systolic pressure and pulmonary artery pressure were normal. Selective right ventriculogram done in one patient showed a small right ventricular cavity. The necropsy findings in this patient confirmed the clinical diagnosis. In the remaining patient angiocardiography showed opacification of a small right ventricular cavity.

Closed-Chest Ventricular Defibrillation with Triangular and Trapezoidal Waveforms

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Triangular and trapezoidal electrical waveforms were utilized as defibrillatory shocks to determine their ability to reverse ventricular fibrillation in anesthetized dogs which had been in fibrillation for 30 seconds. Two triangular waveforms and one trapezoidal waveform were evaluated at peak currents of 10 and 20 amp in 7,200 fibrillation-defibrillation episodes. The percentage effectiveness of each of 60 types of shocks, characterized by having a specific shape, amplitude, and duration, was evaluated by 120 trials (20 on each of six animals).

One of the triangular waveforms consisted of an ascending ramp with a terminal jump to zero, the other of an initial jump followed by a descending ramp. At 20 amp, the effectiveness of both waveforms increased and reached a maximum of almost 100% with increasing duration. The effectiveness of the descending ramp then decreased very rapidly until it was zero at 64 msec. The effectiveness of the ascending ramp, which decreased slowly with increasing duration, was still 96% at 64 msec. The effectiveness of the 10-amp waveform at 64 msec was 0% for the descending ramp and 89% for the ascending ramp.

The trapezoidal waveforms were formed by removing the low-amplitude portion from the 64-msec descending ramp triangular waveforms. The removal of 32 msec of the tail from the 20-amp shock increased the effectiveness of the waveform from 0% to 93%. The removal of 54 msec of the tail from the 10-amp triangular waveform increased the effectiveness from 0% to a maximum of 94%.

Hemodynamic Effects of Angiocardiographic Media with Special Attention to Left Ventricular End-Diastolic Pressure

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Effects of intracardiac angiocardiographic media injections on ventricular rate (VR) and systemic arterial pressure (SAP) are known, but effects on other cardiovascular dynamics, especially left ventricular end-diastolic pressure (LVEDP), need emphasis. Cardiac output (CO), left ventricular pressure (LVP), pulmonary artery pressure (PAP), SAP, and VR were measured before and periodically for 12 minutes after left ventricular injection of 0.6 to 0.8 ml/kg 76% methylglucamine diatrizoate under 400 psi pressure in seven unanesthetized patients (group I). In 14 additional patients (group II), only LVP, SAP, and VR were recorded. Prolonged elevation of LVEDP consistently occurred in group I to an extent unexpected from corresponding flows and pressures. Two cases with decreased postinjection VR failed to demonstrate expected early postinjection increases in CO, while five with unchanged or higher VR had early postinjection CO increases. Late CO in all declined slightly from immediate postinjection values. SAP and PAP rose slightly, except in the two whose VR slowed. Stroke work always increased, but total work failed to increase consistently. In ten group II patients LVEDP increased. Three of four lacking this increase had dilated, noncompliant ventricles, suggesting an inability of end-diastolic fiber length to increase further. VR two minutes postinjection was usually identical or slightly greater compared with preinjection values. There were small variations in SAP two to eight minutes postinjection which were unrelated to VR. Elevated LVEDP persisting eight to ten minutes after ventriculogram independent of CO, VR, or SAP suggests a direct effect on the myocardial fiber tension-pressure response, possibly reflecting altered sympathetic tone, catecholamine release, vascular volume, or direct myocardial toxicity.

Effects of a Program of Graduated Exercises on Patients with Previous Myocardial Infarction

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Eight male subjects (group I) with previous myocardial infarction were studied before and after a 20-week program of graduated exercises. Four control groups were also studied as follows: group II—eight patients with previous myocardial infarction who met weekly for a recreational swim; group III—eight healthy, sedentary men; group IV—eight well-trained, healthy men who took part in a similar program of graduated exercises; and group V—eight healthy men who continued their sedentary habits throughout the study.

All subjects had a physical examination, hemogram, serum protein electrophoresis, serum cholesterol, electrocardiogram, and measurement of subcutaneous fat at six selected sites. Tests of muscular endurance were carried out, and the recovery pulse rate after a progressive step test was recorded. Changes in mood were assessed with a series of psychological tests.

The measurements were repeated at the completion of the study. There were no significant changes in the hemogram, electrocardiogram, protein electrophoresis, and serum cholesterol. Subcutaneous fat measurements showed the greatest change in group I with an average loss of 15.6 mm. Groups III and IV lost 2.0 mm and 4.0 mm respectively, while groups II and V showed an increase of 4.2 mm and 10.3 mm, respectively.

In the tests of muscular endurance, group I also showed the most significant change with an increase of 33.6 units in a standard score. Groups III, IV, and V showed an increase of 11.3, 0.8, and 3.5 units, respectively. Group II was not tested.

Recovery pulse rates following a progressive step test showed a significant improvement in groups I and III.

The two cardiac groups (I and II) experienced the most marked improvement in mood, both subjectively and in the semantic differential test.

Clinical Application of Microcirculation Studies

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In the experimental animal the existence of autoregulation of microcirculation has been established for almost all organ systems. Physiologists have recognized that peripheral blood flow, in order to be completely understood, cannot be analyzed solely in terms of hemodynamic parameters. Flow through minute channels is dependent on additional factors since free flow is no longer uninhibited when the lumen of the carrying channel is about the width of one red cell. Study of the rheology of microcirculation is slowly entering the clinician's orbit.

Recent technical advances have facilitated observation and photography of microcirculation at any site of the human integument. The nail bed, medial malleoli, ventral forearm, and bulbar conjunctiva were examined routinely; areas with overt lesions were also included. To establish a range of physiological variation, 134 healthy subjects were examined. Also studied were 225 patients: 29 with rheumatoid arthritis, seven with scleroderma, 15 with "Raynaud's" acrosclerosis, one with psoriasis, four with psoriatic arthritis, 30 with systemic lupus erythematosus, and 141 with diabetes mellitus. About 3,000 photographs were taken.

In these disease entities certain changes have been observed and documented to be constant and predictable. These changes are not to be interpreted as pathognomonic. They can merely serve as usable parameters for analysis of microcirculation just as the known hemodynamic parameters are used for analysis of macrocirculation.

Staged Correction of Total Transposition of the Great Vessels (P)

William A. Reed, Kansas City, Kansas

The recently described intra-atrial baffle operation for total correction of total transposition of the great vessels makes precise diagnosis and a planned palliative procedure a vital part of eventual correction of the condition.

This report concerns second-stage operations in four patients that had undergone a Blalock-Hanlon procedure (plus pulmonary artery banding in two) two and one-half to four and one-half years previously. Initial palliation was good in each instance. Increasing cyanosis and limitation of exercise tolerance made consideration of total correction necessary. Successful total correction was done in three instances, utilizing the intra-atrial pericardial baffle technique. A previously placed pulmonary artery band was removed in one of these patients. The distal pulmonary artery pressure was normal in each, and all have had excellent functional results, with complete relief of cyanosis and normal exercise tolerance up to one year postoperatively. One patient was explored with total correction intended. Advanced pulmonary vascular changes were found on lung biopsy, as well as marked pulmonary hypertension. Although a pulmonary banding had been done with reduction of distal pressure to 36 mm Hg at the initial procedure, a large ductus arteriosus was not occluded and was probably re-

sponsible for the development of the pulmonary vascular lesions. Total correction was not attempted.

The palliative procedure should include occlusion of ductus arteriosus in most patients and pulmonary banding in selected patients to prevent subsequent pulmonary vascular damage.

Reversibility of Pulmonary Hypertension Following Cardiac Surgery (P)

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Pulmonary hypertension develops in heart disease in three forms: (1) passive pulmonary hypertension caused by elevation of left atrial pressure, (2) hyperkinetic pulmonary hypertension caused by excessive pulmonary blood flow, and (3) reactive elevation of pulmonary vascular resistance (PVR) secondary to either (1) or (2). The first two categories of pulmonary hypertension are automatically eliminated by successful operations; the third category represents a serious complication, the reversibility of which was the subject of this study.

Twenty-five unselected patients with acquired valvular heart disease with PVR in excess of 500 dyne/sec/cm^{-5} underwent serial studies and were compared with a similar series of 12 patients with congenital heart disease and large left-to-right shunts. In acquired heart disease PVR fell from a mean preoperative level of 879 to a postoperative level of 424 dyne/sec/cm^{-5}; in congenital heart disease the corresponding values were 701 and 668 dyne/sec/cm^{-5}. It was determined that in every case of valvular heart disease in which successful reduction of left atrial pressure was accomplished, a significant fall in PVR occurred. In contrast, no consistent changes in PVR were observed after the elimination of left-to-right shunts: PVR fell in some, rose in others, and remained unchanged in the majority of cases.

It is concluded the increased PVR secondary to left atrial hypertension is reversible; high PVR in increased pulmonary flow is irreversible. Left atrial hypertension in addition to high pulmonary flow may be a factor perpetuating high PVR; fall in left atrial pressure is a possible mechanism of regressive pulmonary vascular changes in some cases of congenital heart disease.

Pulmonary Precapillary and Capillary Dilation: A Consequence of Pulmonary Arterial Hypertension (P)

John T. Reeves, James E. Leathers, Jacqueline A. Noonan, and Duane Tweeddale, Lexington, Kentucky

Chronic increase in pulmonary artery pressure and flow is known to alter pulmonary arteries and arterioles, but the changes in precapillaries and capillaries are incompletely described. Microradiographs have demonstrated alveolar capillary networks in relation to their arterial supply. This technique was used to study microcirculation in five patients (aged 12 hours to 50 years) who died without evidence of pulmonary vascular disease and in five patients (aged two months to 30 years) who died with congenital intracardiac shunts. Cardiac catheterization in the latter showed pulmonary artery pressure at systemic levels in all five and pulmonary flows ranging from one to three times normal. Microradiographs and histological sections were correlated. Two patients (ventricular defects two and one-half and seven years) with high pulmonary flow had dilated terminal arterioles in comparison with normal lungs. The precapillaries and initial portion of the alveolar network were dilated two to three times normal. Two young infants (two months and nine months) with atrial left-to-right shunts had less marked dilation of precapillaries and capillaries. Terminal pulmonary arterioles were "knobby." An adult (30 years) with atrial septal defect and cyanosis had plexiform lesions in pulmonary vessels on histological section. Microradiographs showed irregular narrowing of pulmonary arterioles. Pulmonary precapillaries and capillaries were dilated (to ten times normal diameter) and frequently formed complex mazes of thin-walled, tangled vessels. The findings suggest that dilation of pulmonary precapillaries and capillaries occurs when chronically elevated pulmonary arteriolar pressure is transmitted directly to these thin-walled vessels. Furthermore, this concept opposes the traditional view that dilation of capillary vessels does not occur.

Stabilization of Cellular Lysosome Membrane During Cardiopulmonary Bypass (P)

Robert L. Replogle, Alan B. Gazzaniga, and Robert E. Gross, Boston, Massachusetts

Damage to lysosomal membrane may occur during cellular hypoxia secondary to reduced perfusion and/or anoxia. Cortisone and related steroids have been shown to stabilize the cellular lysosomal membrane. This study attempted to determine whether lysosomal membrane damage occurred during cardiopulmonary (CP) bypass and whether this damage could be altered by dexamethasone. Beta-glucuronidase, primarily contained within the lysosome, was used as a "marker" to reflect alterations in the lysosome by measuring serial changes in serum concentration.

Thirty patients were divided into three groups: (1) ten patients undergoing surgery without CP bypass, (2) ten patients undergoing cardiac surgery with CP bypass, and (3) ten patients un-

dergoing cardiac surgery with CP bypass but receiving 80 to 100 mg of dexamethasone in divided doses preoperatively, during bypass, and for 24 hours after bypass. Beta-glucuronidase, LDH, SGOT, and SGPT were measured immediately preoperatively, one hour, four hours, and 24 hours postoperatively.

In group 1 there was no significant alteration in the enzymes measured. In group 2 there was a 77% (875.6 to 1,545.5 μ/100 ml) increase in beta-glucuronidase within four hours after surgery. In group 3 there was a 28% (836.3 to 1,068.4 μ/100 ml) increase in beta-glucuronidase within four hours after surgery. Of the nonlysosomal enzymes measured, there was no appreciable difference between groups 2 and 3.

Cardiopulmonary bypass produces elevation in serum beta-glucuronidase. This elevation is significantly reduced with dexamethasone when given before, during, and after bypass.

Mechanisms of Termination of Abnormal Rhythms as Studied by Continuous Electrocardiographic Monitoring (P)

Ernest W. Reynolds, Jr., Ann Arbor, Michigan, Bruce M. Greenfield, Palo Alto, California, and Walter J. MacDonald, Portland, Oregon

Indirect evidence of the mechanism by which abnormal rhythm begins and terminates was obtained in 110 patients by continuously monitoring the electrocardiogram and instantaneous heart rate.

In atrial flutter increasing the atrial rate from 4 to 26% with digitalis resulted in atrial fibrillation in seven of 16 patients. Five of these subsequently converted to normal rhythm without additional therapy. The remaining patients were given quinidine which decreased the atrial rate 19 to 40%. Those cases (four of nine) in which the atrial rate slowed below the apparently critical rate of 176 characteristically developed electrical asystole, lasting from 1.1 to 2.5 seconds, followed by sinus rhythm. Electrical asystole also characterized spontaneous termination of atrial flutter in three of four patients.

Termination of supraventricular tachycardia was characterized by a 15.4% slowing of the atrial rate in 11 of 15 patients. Sinus pause followed termination of the tachycardia in 12 patients, during which time ventricular escape in the form of random, paired, or coupled ventricular beats were observed in eight of 15 patients, suggesting that re-entry or interference is one of the mechanisms of termination.

Seven (of nine) patients with anomalous atrioventricular excitation treated with quinidine or vagal stimulaton converted abruptly (six) or stepwise (one) to normal conduction, supporting the concept that a single or a few discrete, anomalous conduction pathways are responsible for this entity.

Ventricular tachycardia and ventricular fibrillation were initiated only when a ventricular complex fell on the previous T wave. This observation confirms evidence showing that ventricular vulnerability precedes complete ventricular recovery.

Quantitative Sensing of Instantaneous Blood Flow by a Catheter-Tip Probe Based on Analysis of the Thermostromuhr Calibration Enigma (P)

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Traditional thermostromuhrs are unsuitable for measuring blood flow. A new intravascular velocity probe with platinum coils cooled or heated by flowing blood was mounted on a catheter 0.75 mm by 125 cm. When the probe was operated as a conventional thermostromuhr, high frequency response (3-msec time constant) clarified previous confusion by resolving calibration curves into two components: (1) well-known hyperbolic functions with zero discontinuity and (2) important linear functions of short time constants obvious with pulsatile flows. To eliminate hyperbolic terms, a-c bridge feedback fixed one coil 5° above blood temperature. The power varied directly as velocity to 0.43 exponent. Unheated coils monitored temperature and direction. Centering with retractable arms minimized whip.

Velocity probes and electromagnetic flowmeters agreed when simultaneously calibrated for biphasic sinusoidal and constant flow with piston generator giving known displacement and frequency. The probe linearly transformed velocity to signal from 7 to 200 cm/sec with flow profile, frequency dependence, hysteresis, and noise producing 7% error.

Measurement of blood flow by siliconized probes and cannulating and noncannulating electromagnetic flowmeters in abdominal aortae of dogs gave 85% agreement over-all. Flow, pressure, respiration, electrocardiogram, and cross-sectional area were recorded at different sites under fluoroscopic control with "normal" and zero flows, respiration, drugs, induced extrasystoles, aortic insufficiency, etc. Instantaneous flow volumes ranged from minus 6 to plus 36 ml/sec. Detail was greatest with probe, least with cannulating electromagnetic flowmeter.

Analysis of calibration problems produced a quantitative catheter-tip velocity sensor. In vivo testing documented practicability of sensing instantaneous blood flow volume by catheterization.

Mechanisms of Circulatory Effects of Hypocapnia

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The mechanisms involved in the circulatory responses to hypocapnia were studied in 20 healthy men. After one minute of vigorous overbreathing, arterial CO_2 tension fell to 22 mm Hg, cardiac output (indicator-dilution) rose from 3.0 to 4.1 L/min/m^2, heart rate increased from 70 to 95 beats/min, and mean arterial pressure fell from 96 to 89 mm Hg. At the end of four minutes of overbreathing, arterial pCO_2 was 21 mm Hg, but cardiac output had fallen to 3.6 L/min/m^2, significantly lower than the one-minute value ($P < 0.05$) but higher than control. Heart rate and blood pressure had returned to values insignificantly different from control. In seven subjects after blockade of adrenergic vasoconstriction by intra-arterial phenoxybenzamine, vigorous hyperventilation reduced end-expiratory pCO_2 to minimal values within 20 seconds. Forearm blood flow (venous-occlusion plethysmography) reached maximal levels of two to three times control between the first and second minutes of overbreathing and fell to or below control levels by the fourth minute. Mild hyperventilation, with gradual reduction in arterial pCO_2 to the same level achieved by vigorous overbreathing, did not alter forearm blood flow. Beta adrenergic blockade had no significant effect on the changes in forearm blood flow, cardiac output, or heart rate at one or four minutes of hypocapnia. The results suggest that stimulation of beta adrenergic receptors is not responsible for the circulatory responses to hypocapnia and that rate of change of CO_2 tension may be a more important determinant of cardiovascular response to hyperventilation than is the actual degree of hypocapnia.

Myocardial Arteriolar Alterations in Patients on Phenothiazines

Howard L. Richardson, Kathryn I. Graupner, and Oddist D. Murphree, North Little Rock, Arkansas

The purpose of this paper is to present a summary of the myocardial findings in 72 patients in a neuropsychiatric hospital who expired after phenothiazine therapy. Twenty-seven died suddenly or were found dead in a bed or chair without sign of stress or struggle. Age or dose relationship was apparently not a factor.

The principal lesion found in 69% (47 of 68) of phenothiazine-treated cases was in the arterioles and capillary bed. Ocular microscopic measurements revealed vessels of 0.1 mm down to 0.007 mm to be involved in the pathological alteration. Histologically, the vessels had either a subendothelial protein deposition or endothelial proliferation or smooth muscle hyperplasia. Focal or diffuse myocardial malacia was a common finding in these cases of arteriolar alterations and was found to be drug related.

In young patients with sudden death, it was advantageous to do serial block sections of the heart. The coronary vessels were remarkably free from occlusion or atheroma, yet the intramyocardial arterioles and capillary bed showed extreme alterations. Histochemical preparations were routinely performed and aided in the demonstration of the zones of myocardial malacia.

Experimentally, the identical intramyocardial arteriolar vascular and capillary bed lesion was produced in animals. Phenothiazines were administered in a similar manner as when given to humans.

Of extreme concern are the possible aftereffects that may result in children when these myocardial hypotensive drugs are used.

Acute Severe Mitral Regurgitation Secondary to Ruptured Chordae Tendineae: A Distinctive Clinicopathological Syndrome (P)

William C. Roberts, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Maryland

Ten patients with severe mitral regurgitation caused by rupture of one or more chordae tendineae were studied, and analysis of clinical, hemodynamic, and pathological features disclosed a number of differences from those commonly noted in patients with the more usual form of mitral regurgitation. The patients with ruptured chordae tendineae usually showed little left atrial enlargement, were in sinus rhythm, gave no history of acute rheumatic fever, and had seve.ely elevated pulmonary arterial and left atrial pressures. The symptoms of cardiac decompensation generally appeared abruptly and were usually present for only several months before they led to the patient's death or necessitated operative treatment. In six patients bacterial endocarditis was proven to be the cause of the chordal rupture, and in the other four as well, it was probably the etiological factor. The mitral valves at autopsy or after operative excision showed no gross abnormalities other than the ruptured chordae and mild thickening of the adjacent leaflet. There was no associated aortic valve disease. It is suggested that bacterial endocarditis occurring in hearts without detectable anatomical valvular abnormalities is an important cause of chordal rupture. The majority of patients with ruptured chordae cannot sustain the acutely imposed hemodynamic burden for periods of time sufficient to allow the increase in left atrial compliance so

frequently observed in patients with chronic rheumatic mitral regurgitation. This situation results in a distinctive clinicopathological syndrome, characterized by a gross disproportion between left atrial size and pressure, an explosive development of obstructive pulmonary vascular changes, and right-heart failure.

Tricuspid Leaflet Aortic Valve Prosthesis (P)

Benson B. Roe, Paul B. Kelly, Jr., and John L. Myers, San Francisco, California

Three basic types of prosthetic aortic valves have been developed: (1) the caged ball, (2) hinged mechanisms, and (3) flexible leaflets. The caged ball valve has gained recent acceptance because its mechanism is simple and reliable, but it has serious practical and theoretical drawbacks. This report describes the development and testing over a ten-year period of a precision-molded tricuspid subcoronary leaflet valve. The leaflet prosthesis is a casting of an exceptionally durable elastomer (silicone rubber) into which a metal band and cloth suturing jacket are incorporated. Three thin (0.017-inch) leaflets are supported in ideal alignment so that they open symmetrically and close in perfect apposition. Functional performance during implantation in animals, stress testing in pulse duplicators, and high-speed photography have demonstrated (1) minimal outflow tract obstruction, (2) comparatively large internal orifice-outside diameter ratio, (3) laminar flow and reduced downstream turbulence, and (4) durability (five years in humans, four years in dogs, and 19 "years" in pulse simulator). Additional characteristics of this valve are as follows: (1) low vertical profile, (2) light weight, low inertia, and (3) silence; furthermore, an antithrombogenic coating (GOTT) can be applied to the entire surface of the valve. Selective clinical trial in 15 patients between 1960 and 1962 has resulted in five long-term survivors. Angiocardiography and left ventricular catheterization in three patients demonstrated satisfactory function and competence up to five years after insertion of the valve. The aortic leaflet valve should have wider clinical application, and in patients with a narrow aortic outflow tract, its use is essential.

Effect of Selective Cation Depletion on Cardiac Function

Jerry L. Rosenbaum, Lamberto G. Bentivoglio, and Harry Goldberg, Philadelphia, Pennsylvania

The effect on cardiovascular function of sudden reduction of the serum concentration of calcium, magnesium, and potassium was determined in 16 normal dogs, while two had a sham procedure. A femoral arteriovenous shunt was produced for 30 minutes, flowing through a 250-g sodium Dowex ion exchange column with mean flow rates of 150 ml/min. Selective removal of each cation was accomplished by simultaneous reinfusion of the other two. Cardiac output (CO) by the dye-dilution techniques and systemic arterial pressure (BP) were determined before, immediately after, and one-half, one, two, and three hours after each perfusion. In four dogs all cation concentrations were lowered simultaneously (group I); in three other groups of four dogs each, serum calcium (group II), magnesium (group III), and potassium (group IV) were reduced selectively.

Serum calcium, magnesium, and potassium concentrations were reduced 32%, 30%, and 29%, respectively, following perfusion. In groups I, II, and III, mean BP decreased over 20% 30 minutes after perfusion, with gradual return to normal. By the third hour CO decreased 30 to 50% in groups I, II, and III, and total systemic resistance (TSR) increased 30 to 60%. No appreciable cardiodynamic effects were noted in the sham group and in group IV. These observations suggest that in dogs a sudden reduction in serum calcium and/or magnesium but not potassium concentrations results in an immediate but transient fall in mean BP, a progressive fall in CO, and a delayed rise in TSR within three hours.

Comparison of Uncontrolled and Double-Blind Controlled I^{131} in Angina Pectoris

Benjamin A. Rosenberg and Sanford Sarney, Brooklyn, New York

In an uncontrolled study 20 patients, 14 males and six females, of mean age 56, received an average initial dose of 25.8 mc of I^{131} (7 to 35). An average supplemental dose of 12 mc (5 to 15) was administered to nine cases. Follow-up was conducted an average 30.2 months (five to 101). Improvement in nitroglycerin requirement and/or exercise tolerance was noted at 79% (48 of 61) of patient visits. Thyroiditis occurred in none, myxedema in seven, and death in one from myocardial infarction.

In the double-blind study there were 21 patients, 12 males and nine females, of mean age 63. One received placebo only and ten I^{131} alone. Cross-overs of placebo to I^{131} occurred in nine and the converse in one. Average initial dose was 27.2 mc (4 to 30) and supplemental dose 11 mc (4 to 30). Follow-up was conducted an average of 22.3 months (three to 33). Improvement in nitroglycerin requirement and/or exercise tolerance was noted at 63% (63 of 100) of all patient visits for the I^{131} group and 66% (31 of 47) for the placebo group ($X^2c(1) = 0.026$, $P < 0.95$). Clinical improvement could not be cor-

related with changes in cholesterol, basal metabolic rate, or weight in either treatment group. There was a significant correlation of I^{131} treatment with depression of iodine uptake ($X^2c(1) = 13.24$, $P < 0.001$). Thyroiditis occurred in none, myxedema in three, and death in six, one from massive postoperative gastrointestinal hemorrhage, one from ruptured aneurysm, and four from coronary occlusion/myocardial infarction. Two of the latter subgroup received placebo, one followed by I^{131}.

Clinical and Hemodynamic Effects of Chronic Administration of Reserpine in Patients with Idiopathic Hypertrophic Subaortic Stenosis

Robert Rosenblum, Jerome Cooper, and Stephen J. Gulotta, New York, New York

A study was undertaken to evaluate the effect of chronic administration of reserpine to patients with hemodynamically proven idiopathic hypertrophic subaortic stenosis (IHSS). Twelve patients were maintained on 0.25 mg of reserpine daily. Larger doses could not be tolerated because of postural hypotension. Subjective improvement occurred in eight, a decrease in atypical chest pain in five of eight in whom it was present, and an increase in effort tolerance in three of four patients. There was no relationship between subjective improvement and severity of left ventricular-brachial artery (LV-BA) gradient. One asymptomatic patient with no resting LV-BA gradient had a definite decrease in effort tolerance. Four patients were recatheterized two to eight months after reserpinization. A decrease in BA upstroke velocity (dp/dt mm Hg/sec) from 1,175 to 800 and 1,500 to 590 was demonstrated in two patients, and two had no changes (540 to 480, 900 to 850). A decrease in LV and BA pressures was noted in three patients, and in one of three (dp/dt 1,175), there was a decrease in LV-BA gradient (100 to 30 mm Hg) with no change in cardiac index (CI). No patient demonstrated a decrease in CI, but a constant, although insignificant, increase in CI was noted in all patients (5 to 12%). No patient had an increased sensitivity to iv isoproterenol. A decrease in the calculated LV outflow area occurred in two patients during isoproterenol infusion. Too cautious an administration of isoproterenol in two patients might have been responsible for the lack of change in LV-BA gradient, although the CI rose 10 and 25%. In one patient (dp/dt 1,500), the acute iv administration of reserpine (1.5 mg) prior to chronic administration of the drug had no effect on LV-BA pressures, gradients, dp/dt, or CI. One patient with both fixed and functional LV obstruction showed no changes in any of the measured parameters. These preliminary data suggest that reserpine decreases the hyperkinetic aspects of IHSS when present.

Heart-Forming Region of the Chick Embryo: A Radioautographic Study (P)

Glenn C. Rosenquist, Baltimore, Maryland

Chick blastoderms (*Gallus gallus*) were explanted by the technique of New (endoderm side up). A solution of tritiated thymidine in chick Ringer's saline was applied to the hypoblast surface of donor embryos (1 μc/embryo). These embryos were incubated for two to ten hours. At stage 5 to 8, endoderm-mesoderm fragments were removed from the heart-forming regions of the donor blastoderm by individually dissecting them away from the overlying epiblast and transferring them to separate nonlabeled recipient embryos of similar staging which had been prepared by removing the homologous endoderm-mesoderm area. Within one to two hours of reincubation, the graft had healed in completely.

Reconstructions prepared from radioautographed serial sections were used to follow the distribution of labeled cells in hearts of embryos subsequently developing to stage 10 (heart beat begins) to limb bud stages (approximately three days). Grafted mesoderm cells participated normally in development of the heart through these stages.

The heart forms entirely from the splanchnic mesoderm, with the exception of the areas where the cardinal veins enter the sinus, which may receive some cells from the somatic mesoderm. Of the heart-forming regions the most cephalic and medial (head of crescent) cells become endothelial, medial cells become dorsal mesocardium and myocardium, while lateral cells swing to the midline and contribute cells to ventral mesocardium and myocardium. Loop formation can be accurately followed since labeled ventral myocardium (anatomical midline of single heart tube) continues to appear at this junction after the heart breaks away from its ventral mesenteric attachments.

Circulatory Changes in the Diving Turtle

Gordon Ross and Fred N. White, Los Angeles, California

Electromagnetic flowmeters previously implanted about an aorta and pulmonary artery were used to study simultaneously the changes produced by diving in the systemic and pulmonary circulations of free-living fresh-water turtles. Aortic and pulmonary pressures were obtained via indwelling catheters. In air, pulmonary flow exceeded systemic flow. Instantaneous pulmonary pressure and

flow curves resembled each other, but aortic flow and pressure contours differed, and a brief early diastolic aortic backflow occurred. Ejection into the pulmonary artery preceded that into the aorta by approximately 0.12 second. During forced submersion the magnitude of the left-to-right shunt gradually diminished. Following submersion profound bradycardia developed after an interval which varied from 12 to 240 minutes. At this time stroke aortic flow greatly exceeded stroke pulmonary flow. After surfacing in air, oxygen, or nitrogen, the bradycardia was abolished as soon as the first breath was taken, and heart rate, pressures, and flows returned to the pre-dive condition within two minutes. Resubmersion within a few minutes of a previous dive produced immediate bradycardia. When the animals surfaced into 100% carbon dioxide, the bradycardia and the pressure and flow changes associated with submersion persisted. It is concluded that in turtles an important circulatory adaptation to diving is the production of a right-to-left shunt. In contrast to mammals, bradycardia develops late. Hypercarbia appears to be an important factor in producing the changes observed.

Effect of Quinidine on Competitive Cardiac Pacing (P)

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Considerable controversy exists regarding the hazard of producing repetitive ventricular arrhythmias during competitive cardiac pacing. Some investigators have suggested the use of quinidine to reduce myocardial irritability in this situation and to prevent ventricular fibrillation. The purpose of this study was to observe competitive cardiac pacing in dogs and the effect of quinidine on this phenomenon.

Transvenous bipolar catheter pacemakers were inserted in the right ventricle of 20 mongrel dogs in sinus rhythm. Pacemaker stimuli were delivered at a rate of 120 per minute, energy output of 6 ma, and duration of 2 msec. After 30 minutes of competitive pacing, 5 to 10 mg/kg of quinidine were given to each animal intravenously.

No ventricular arrhythmias were detected in the initial observation period, although pacemaker stimuli repeatedly fell in the vulnerable phase of sinus beats. However, repetitive ventricular firing and ventricular fibrillation occurred in 14 dogs after administration of quinidine. In all instances the ventricular arrhythmias were initiated by pacemaker stimuli that fell in the vulnerable period of sinus beats or of spontaneous ventricular premature systoles.

Competitive pacing between the sinus node and conventional electronic stimuli did not result in ventricular arrhythmias in normal dogs. However, repetitive ventricular firing and ventricular fibrillation occurred in 14 of 20 dogs after intravenous quinidine. It may be that quinidine lowers the fibrillation threshold by prolonging the refractory period and increasing the asynchronous nature of repolarization. In any event it is our contention that quinidine should not be used in patients who have electronic pacemakers competing with normally conducted beats.

Transposition of the Great Vessels with Pulmonary Stenosis, with Special Reference to Differentiation of This Malformation from Tetralogy of Fallot and Double-Outlet Right Ventricle with Pulmonary Stenosis

Richard D. Rowe, Ali Mehrizi, Grover M. Hutchins, and Gordon M. Folger, Jr., Baltimore, Maryland

Transposition of the great vessels with pulmonary stenosis is a rare malformation. At the Cardiac Clinic of the Johns Hopkins Hospital, we have observed 15 cases of this anomaly, and the clinicopathological correlation of these cases is the subject of this report. There were 12 males and two females. The sex and age of one patient are not known. Ages ranged from 11 days to 19 years. All the patients had severe cyanosis from birth, squatting was not a usual feature, and cyanotic spells were infrequent. Chest X-ray showed moderate cardiac enlargement, and the electrocardiogram demonstrated combined ventricular hypertrophy and right atrial enlargement in all instances.

The malformation calls for differentiation from tetralogy of Fallot and double-outlet right ventricle with pulmonary stenosis. The absence of cyanotic spells and infrequent squatting with presence of combined ventricular hypertrophy on electrocardiogram and moderate cardiac enlargement on X-ray exclude the possibility of tetralogy. The clinical feature in this malformation is rather similar to that of double-outlet right ventricle with pulmonary stenosis, but the absence of complete bundle-branch block and first degree atrioventricular block, which is observed commonly in patients with double-outlet right ventricle with pulmonary stenosis, distinguishes between the two malformations.

Finally, surgery (Blalock-Hanlon and Blalock-Taussig operations) led to congestive cardiac failure and death in the immediate postoperative period in the majority of cases. In those who survived the operation, clinical symptoms, such as exercise tolerance and degree of cyanosis, growth, and development, have not been significantly improved.

Cardiac Output in Man During Exercise at Normal and High Ambient Temperatures (P)

Loring B. Rowell, Herbert J. Marx, Robert D. Conn, and Robert A. Bruce, Seattle, Washington

Experiments were designed to assess how cardiac output adjusts to competitive metabolic and thermal requirements of exercise and heat stress since recent studies showed greater decrements in hepatic blood flow during work at 110 F than at 78 F. In six normal, non-heat-acclimatized young men, cardiac output was determined seven times during each of four intensities of exercise at 78 F and 110 F (56 measurements per man). Exercise (15 minutes) required from 45 to 86% of maximal oxygen intake at both temperatures. Indocyanine-green was injected into the right atrium and sampled from the aortic arch. During the first two levels of exercise, mean cardiac outputs (168 measurements) were identical at both temperatures, while two men showed a decrease and two an increase during the second level of exercise at 110 F. With increasing severity of exercise, cardiac output was lower at a given oxygen intake at 110 F than at 78 F. Three subjects approached maximal heart rates during the third level of exercise and failed to increase cardiac output for the final level of exercise, which was accomplished with normal increment in oxygen intake but widened A-VO_2 difference. Stroke volume remained constant with respect to time and work intensity but was 20 ml/beat lower at 110 F. Initial determinations of central blood volume (two men) showed it to be significantly reduced at 110 F. Added demands for heat dissipation during exercise are met by repartitioning cardiac output rather than by increasing it.

Distribution of the Circulation in the Fetus in Utero (P)

Abraham M. Rudolph, Michael Heymann, and Gershon Hait, New York, New York

Previous studies of the fetal circulation have been conducted on the fetus delivered from the uterus but still attached to the placenta. The degree to which the experimental techniques used affect normal physiology of the circulation has not been assessed.

Observations have been made on the distribution of blood flow to all major fetal organs and to the placenta in the lamb in utero. Polyvinyl arterial and venous catheters were inserted into a limb exposed through a small uterine incision. The uterus and abdomen were closed and the catheters exteriorized. Fetal and maternal arterial pH, pO_2, and pCO_2 were measured. A single injection of radioactively labeled microspheres of 50 μ diameter was made into the venous catheter. The lamb was delivered, and total radioactivity in various organs was measured by a well scintillator detector. Microspheres were distributed in proportion to flow, and no loss of isotope into the mother was detected. Organ flows could be expressed as percentage of total flow or related to placental flow. In four lambs forelimb injections (superior vena caval return) showed only minute flows to the heart and brain. Pulmonary flow varied widely (11 to 360% of placental flow), while kidney flow was 2 to 5% of placental flow. In four other lambs hindlimb injections (inferior vena caval return) showed the following organ flows as percentage of placental flow: brain 5 to 8, heart 6 to 11, lungs 2 to 7, kidneys 3 to 20. The flows have been related to fetal acid-base status and oxygenation. The fetal liver received negligible flow from the aorta but an enormous flow from the umbilical veins.

Aortic Regurgitation: Angiographic Study of Its Natural History Following Mitral Valvulotomy and Its Effect on Postoperative Prognosis

Vincent Runco, Hugh S. Levin, Omaha, Nebraska, Charles F. Wooley, Columbus, Ohio, and Richard W. Booth, Omaha, Nebraska

The effect of mitral valvulotomy on coexisting aortic regurgitation and the severity of aortic regurgitation permitting isolated mitral valve repair have not been adequately defined. The unreliability of conclusions based on clinical evaluation alone, especially regarding aortic regurgitation, stimulated the present investigation of 25 patients with "tight" mitral stenosis proven by catheterization prior to closed mitral valvulotomy. Preoperative aortic valvulography performed in 21 with basal diastolic murmurs demonstrated one to three plus aortic regurgitation (zero to four plus scale). Catheterization or clinical evaluation postoperatively indicated that all patients had successful relief of the mitral valve obstruction. Aortic valvulography repeated two weeks to 20 months after surgery in nine patients showed some increase in aortic regurgitation in six, three of whom had no further increase on a third valvulogram 20 to 30 months later. Four additional patients without clinical indications for preoperative valvulography developed auscultatory "unmasked" aortic regurgitation following surgery which was confirmed angiographically.

Although serial angiograms, within the limitations of the technique, frequently demonstrated increased aortic regurgitation following mitral valvulotomy, all patients with two plus regurgitation or less obtained an excellent (19) or good (five) objective and clinical result four months to five years postoperatively. One patient whose aortic regurgitation increased from three to four plus expired ten months postoperatively.

At least for the period encompassed, this study indicates that mild to moderate aortic regurgitation does not adversely affect the results of closed mitral valvulotomy and should better define the indications for correction of aortic regurgitation in candidates for mitral valve surgery.

Transcutaneous Doppler Flowmeters for Nondestructive Studies of Peripheral Vascular Function

Robert F. Rushmer, H. Fred Stegall, and Ernest P. McCutcheon, Seattle, Washington

Recent advances in instrumentation technology have initiated revolutionary changes in the diagnosis and evaluation of cardiovascular disease in research laboratories and in hospitals but have had little impact in routine practice. Nondestructive testing techniques for general application are urgently needed to extract objective information from within the body without hazard, pain, or damage to the skin. For example, ultrasonic devices are now available for the registration of the position, size, and displacement of internal structures and for monitoring blood flow velocity from external transducers. The transcutaneous Doppler flowmeter has been developed as a convenient portable instrument to provide easily interpreted signals related to blood flow velocity in superficial or deep vascular channels. This device, in conjunction with other nondestructive techniques for monitoring dimensions and flow, has produced more comprehensive descriptions of cardiovascular responses, such as the peripheral vasoconstriction and redistribution of blood in the extremities during passive tilting. Further, venous occlusion cuffs (20 to 50 mm Hg) have been demonstrated to produce peripheral vasoconstriction and diversion of blood flow from superficial veins. Clinical evaluation of the transcutaneous Doppler flowmeter has indicated potential usefulness in the detection of fetal flow rates at early stages of pregnancy (i.e., ten to 12 weeks), evaluation of the sites of arterial occlusion, and the state of collateral flow in vascular diseases of the extremities. Doppler signals from the precordium are very complex since the movement of heart walls and valves are superimposed on flow signals, rendering interpretation difficult.

Evaluation of Infusion Therapy for Venous Thrombosis (P)

H. E. Russell, R. R. Bradham, and William H. Lee, Jr., Charleston, South Carolina

Previous experiments suggested that the mode of administration of "antithrombotic" agents compromised an important factor in the inhibition of venous clotting. The experiments herein reported were designed to test this hypothesis.

In each of four groups of ten mongrel dogs, a technique of inducing thrombosis by passage of electrical current was applied to both femoral veins. Simultaneously, each group received an intravenous infusion of one of four solutions into a distal tributary of one femoral vein. Each animal thus offered a damaged vein exposed to direct perfusion of the agent and a contralateral vein which was perfused only by systemic circulation of the drug. The agents used were (a) saline (0.45%) in dextrose (2.5%), (b) 10% low molecular weight dextran (40,000) in saline, (c) 6% dextran (75,000) in saline, and (d) 6% hydroxyethyl starch in saline. Dosage of all drugs was a volume equal to 2% of the body weight of the animal. Six hours after treatment, the veins were opened and inspected, and the extent of thrombosis was evaluated. The results demonstrated the following: (1) Direct infusion of the solutions was clearly superior to systemic administration in preventing thrombosis ($P < 0.01$). (2) In the veins exposed only to systemic administration of the agents, the plasma expanders offered protection against thrombosis when compared with the control dextrose/saline infusion. (3) In the directly perfused veins no agent demonstrated statistically significant benefit which was superior to the control dextrose/saline solution.

Small Bowel Ulcerations Associated with Enteric-Coated Potassium Chloride

R. Patterson Russell, Nathan H. Carliner, and John H. Yardley, Baltimore, Maryland

Nine cases of small bowel ulcerations were found associated with the administration of enteric-coated potassium chloride (KCl). Two cases were discovered at postmortem examination, while seven were detected at surgery. The ulcerations were circumferential and solitary, leading to stenosis and obstruction, although in two cases there were multiple circumferential and punctate ulcers and in one case multiple punctate ulcers leading to perforation.

Enteric-coated KCl in combination with a benzothiadiazine diuretic was administered to eight patients with a history of hypertensive cardiovascular disease. One patient with an obstructing carcinoma of the colon developed hypokalemia while on steroids and received enteric-coated KCl tablets.

A random survey of 200 hypertensive patients undergoing therapy revealed that 183 had been exposed to a benzothiadiazine diuretic at some time during the past five years. Of this group 101 had not received any supplementary potassium, and there were no instances of small bowel ulceration. In the group of 82 patients who had

been exposed to some form of enteric-coated KCl, there were two cases of circumferential small bowel ulceration, an incidence of 2.4% (two of 82).

These observations are in accord with recent reports which have demonstrated ulcerations of the small bowel in dogs and monkeys following administration of enteric-coated KCl, either alone or in combination with benzothiadiazine diuretics, and they suggest that when supplemental KCl is required, it should be administered in the liquid form or as a tablet which is not enteric-coated.

Pentaerythritol Tetranitrate in Acute Myocardial Infarction (P)

Thomas J. Ryan and Mortimer Schnee, Boston, Massachusetts

Lumb has reported an increased survival of pigs undergoing acute myocardial infarction if pentaerythritol tetranitrate (PETN) was administered shortly after the damage. To test the effectiveness of this drug in man, PETN, 80 mg, sustained action, or an identical placebo was administered orally to 147 consecutive patients suspected of having an acute myocardial infarction on admission in a randomized, double-blind fashion. On the basis of clinical picture, electrocardiogram, and laboratory data, 107 patients were subsequently considered to have had unequivocal acute myocardial infarction and to have taken the medication every 12 hours during their hospital stay. Of these, 21 died, with an over-all mortality of 20% (21 of 107). There was no significant difference between the mortality of the PETN group, 17% (nine of 53), and the placebo group, 22% (12 of 54), $P < 0.5$. In a comparison of factors, such as death within seven days, previous infarct, location of infarct, obesity, hypertension, congestive failure, shock, use of anticoagulants, age, and sex, there were no significant differences between the two groups. Postmortem coronary artery injections were performed in four of the PETN group and failed to demonstrate augmented collateral circulation when compared with controls. Resolution of electrocardiographic changes, duration of hospital stay, and narcotic requirements likewise were not significantly different for the two groups.

It is concluded that PETN has no significant influence on the survival rate of patients during the acute phase of a myocardial infarction.

Value of Microsurgical Methods in Small Vessel Anastomosis and Grafting (P)

John R. Sadd, John T. Mendenhall, and Vincent L. Gott, Madison, Wisconsin

Vessels smaller than 3 mm in diameter can apparently be successfully anastomosed, but attempts to replace segments of such vessels with prostheses have failed. Cicatricial stenosis of suture lines resulting from intimal trauma has been blamed for many failures. Nonsuture techniques have reportedly met with considerable technical difficulties. The microsurgical technique apparently owes its success to minimization of intimal trauma by meticulous coaptation of vessel ends with fine suture material. The purpose of this study was to attempt to confirm the value of this technique and its effect on prosthetic replacement of segments of small vessels.

Carotid, brachial, and dorsalis pedis arteries of 30- to 35-lb. dogs were studied. An operating microscope and standard instruments were used. All suture material was 7-0 arterial silk, and grafts were woven, crimped Teflon 5/32 inch diameter. No anticoagulants were employed. Vessel diameters were measured with an ocular micrometer prior to adventitial dissection. Vessels were examined for patency by re-exploration followed by removal for pathological examination. Canine brachial arteries averaging 2.5 mm in diameter were sectioned and anastomosed. Eight of ten were patent at one month. Similarly, nine of ten 1.5-mm dorsalis pedis arteries were open at two months. Eight of 20 carotid prostheses 5 cm in length were patent at two months. Two of ten prostheses placed with S-shaped anastomoses to minimize stenosis were open at two months. Autogenous vein grafts 5 cm long, placed in canine dorsalis pedis arteries, have all been shown radiographically to be open at one month and are being followed.

Microsurgical techniques permit anastomosis of vessels the size of a human digital artery. Short segments of autogenous vein can apparently be grafted into such vessels. Refined techniques do not significantly alter prosthesis failure rates despite application of an anastomotic technique which minimizes suture line stenosis.

Hyperbaric Oxygenation Therapy of Acute Cerebral Vascular Insufficiency (P)

Herbert A. Saltzman, Banks Anderson, Jr., Robert E. Whalen, Albert Heyman, and Herbert O. Sieker, Durham, North Carolina

Remarkable increases in blood oxygen transport and tension (pO_2) can be achieved during hyperbaric oxygenation. If this increase in oxygen delivery can be translated safely into more effective tissue oxygenation, central nervous system ischemic damage may be reversed or prevented. For this reason the circulatory and functional responses of the nervous system to hyperbaric oxygen have been evaluated in animals, normal subjects, and patients during retinal and cerebral ischemia. Although high oxygen pressures are as-

sociated with striking vasoconstriction, augmented blood-oxygen content compensates easily for any loss of oxygen transport from reduced perfusion. This net gain in tissue oxygenation is indicated by the increased persistence of vision and normal cerebral electrical activity when retinal or cerebral perfusion is interrupted during hyperoxygenation. Of 14 patients with recent cerebral infarcts, five have responded favorably to hyperbaric oxygenation with improved mentation and diminution of paralysis. In one instance improvement persisted after decompression; in the remaining four cases, however, the favorable responses proved to be temporary, even though one of these patients displayed reversal of paralysis during hyperoxygenation on two separate occasions. Concomitant polarographic measurements confirmed the anticipated rise in oxygen tension to more than 1,500 mm Hg in arterial blood and beyond 80 mm Hg in cerebral venous blood. Although the over-all therapeutic gain from treatment was small, the demonstration of immediate improvement in patients with recent neurological deficits offers encouragement in attempting correction of acute cerebral vascular insufficiency.

Hemodynamic Effects of Atrial and Ventricular Tachycardias (P)

Philip Samet, William H. Bernstein, and Alfredo Lopez, Miami Beach, Florida

Current interest in the therapy of complete heart block with both synchronous and asynchronous implanted pacemakers has aroused interest in the hemodynamic contribution of synchronized atrial activity to ventricular activity. The problem has been approached in the present study by an analysis of six patients with complete heart block and 54 with normal sinus rhythm. In the latter subjects a bipolar electrode catheter was employed to compare the hemodynamic findings during right ventricular and right atrial pacing. A total of 154 paired comparisons of cardiac index were made at similar ventricular rates greater than the control sinus rates. The average cardiac index during atrial pacing was 2.76 L/min/m^2; during ventricular pacing the index fell to 2.27 L/min/m^2. This difference is highly significant ($P < 0.001$). The same results were obtained when the data were divided into three groups: ventricular rates 60 to 89, 90 to 109, and 110 to 140. In the 60 to 89 ventricular rate group the average ventricular pacing index was 2.13 L/min/m^2; during atrial pacing the average index was 2.66. In the 90 to 109 group the atrial pacing index was 2.70, the ventricular pacing index 2.24 L/min/m^2. In the 110 to 140 group the ventricular pacing index was 2.27, the atrial 2.80 L/min/m^2. These differences were all significant ($P < 0.001$ for all three groups). In addition to changes in flows, characteristic abnormal alterations in right- and left-heart pressure curves were noted during ventricular pacing but not during atrial pacing.

Tricuspid Stenosis: A Difficult Diagnosis in the Presence of Atrial Fibrillation

Charles A. Sanders, J. Warren Harthorne, Roman W. DeSanctis, and W. Gerald Austen, Boston, Massachusetts

Tricuspid stenosis (TS) may often be diagnosed by careful physical examination alone if normal sinus rhythm is present. With the onset of atrial fibrillation, the classic physical and hemodynamic findings may be altered and the diagnosis overlooked despite direct pressure measurement across the tricuspid valve. This report concerns ten patients (nine females, one male) with moderate to severe TS complicated by atrial fibrillation. There was associated severe mitral stenosis in every case. In only two patients was TS suspected prior to right-heart catheterization. Pullback recordings from the right ventricle (RV) to the right atrium (RA) revealed a distinct diastolic pressure gradient in only three cases (including the two mentioned above). When simultaneous RV and RA pressures were obtained (usually via a double lumen catheter), a diastolic mean gradient (average 5 mm Hg) was found in every patient. This gradient could be enhanced by inspiration, exercise, or amyl nitrite (average 9 mm Hg). With expiration the gradient decreased and was occasionally abolished (average 2.6 mm Hg). End-diastolic gradients varied, depending on the length of the diastolic filling period (range 0 to 13 mm Hg). Reduction in cardiac output was a uniform finding. The diagnosis of significant TS was confirmed in the eight patients undergoing open-heart surgery. This experience suggests that with atrial fibrillation severe TS may frequently go undetected if only pullback tracings from RV to RA are relied on. If the presence of significant TS is not appreciated, subsequent surgical treatment will be inadequate. It is recommended that simultaneous pressure measurements between the RV and RA be performed routinely, particularly in those patients with mitral valve disease.

New Method for the Determination of Total Cerebral Blood Flow in Man (P)

Leo A. Sapirstein, Stanford, California

An important supplementary procedure in the diagnosis of stroke may be the determination of the cerebral blood flow, either regionally or to the whole brain. The Kety method and gas wash-

out methods, which have proved their suitability for cerebral blood flow measurements in normals, unfortunately yield results which may not be applicable in persons with impaired cerebral circulation. The reasons for this difficulty are discussed in the report. A method for the measurement of cerebral blood flow which avoids the difficulties described in the above critique has been developed and applied to man. It is based on the indicator fractionation technique, whose basic premise is that intravascularly injected materials are originally distributed among the organs in proportion to the blood flow through them. The application of this technique to the estimation of cerebral blood flow in normal and hyperventilating subjects and its possible application to the detection of impaired circulation in the stroke patient are presented in the report.

Cardiopulmonary Alterations in Acute Pulmonary Thromboembolism

Arthur A. Sasahara, Gerard M. Tremblay, and O. Stevens Leland, Jr., West Roxbury, Massachusetts

Selective pulmonary angiography has provided the opportunity to obtain hemodynamic data in 43 patients with acute pulmonary thromboembolism.

Thirty-one had pre-existing cardiopulmonary disease. Right ventricular end-diastolic pressure was more than 8 mm Hg in 28 patients. Low cardiac index (less than 2.5 L/min/m^2) in 13 and increased arteriovenous oxygen difference (more than 4.0 vol %) in 17 were observed in 21 patients. Pulmonary hypertension [mean pulmonary artery pressure (PAm) more than 20 mm Hg] was present in 29 patients. One-third of these had pressures greater than 40 and were in right-heart failure. The pulmonary arteriolar resistance measured in 13 patients ranged from 135 to 1,440 dyne/sec/cm^{-5}. Acetylcholine was infused into the pulmonary artery of 15 patients, resulting in lowering of the PAm pressure of 16% (range 4 to 42%). Inhalation of 100% oxygen by 24 patients resulted in a mean fall of 20% (range 10 to 38%).

The degree of impairment of oxygenation was assessed in 34 patients. Thirty-one had hypoxemia [arterial oxygen tension (aPO_2) less than 80 mm Hg; range 32 to 80 mm Hg], which was not corrected by inhalation of 100% oxygen in 21 patients, suggesting the importance of venous admixture. The degree of hypoxemia did not correlate well with the level of pulmonary hypertension but did with the pulmonary diffusing capacity, which was decreased in 17 of 25 patients.

Acute pulmonary thromboembolism is frequently associated with right-heart failure, pulmonary hypertension, elevated pulmonary arteriolar resistance, and hypoxemia, which are probably due to the interplay of mechanical, passive, and vasoactive factors.

Cardiac Pacing by Means of Electrical Energy Derived Directly from the Heart

Victor Satinsky, Leonard S. Dreifus, Phillipe Racine, Harold L. Massie, and Luther Reynolds, Philadelphia, Pennsylvania

The ultimate goal in cardiac pacemaker design should embrace two significant features: it should be free of (1) battery dependence and (2) wire connections, which together account for nearly all of the present-day failures. Experiments have been carried out which promise to fulfill these criteria.

Electrical energy (0.5 to 0.6 v) is derived directly from the surface of the heart by means of two surface electrodes, one consisting of platinum black and the other of high speed stainless steel. This voltage is directed to an electronic pulse-forming circuit which is specially designed for low-voltage input and capable of delivering amplified power to bipolar stimulating cardiac electrodes. By means of this pacemaker, it was possible, first in ten dogs and subsequently in two patients, to pace the ventricle at various rates, utilizing 1.5 v of 2-msec duration with an energy yield of approximately 10 microjoules per pulse. Whether the platinum black-stainless steel electrodes act as a modified fuel cell or mainly galvanically is under study. However, since the electrical energy is derived directly from the myocardium and amplified, pulsed, and returned to the myocardium, the feasibility of autocardiac pacing becomes apparent.

Replacement Versus Reconstruction of the Aortic Valve (P)

J. Gordon Scannell and W. Gerald Austen, Boston, Massachusetts

This is a report of the entire experience with open operation for aortic valve disease in adult patients at the Massachusetts General Hospital from 1957 to May 1965, a total of 266 patients. The 152 patients who underwent debridement and incision (mortality 25%) have been compared with 114 patients who had aortic valve replacement (Starr) during the past two years (mortality 17%).

Long-term follow-up data are presented on all but one patient who survived valvuloplasty prior to October, 1961 (51 patients). The three-year survival of this group was 86%. Fourteen have come to reoperation. It is clear that while the result of debridement valvuloplasty may be worth

while at three years, in very few will it continue to be satisfactory at five or more years. This observation has been confirmed by catheterization studies.

Except in unusual circumstances valve replacement has supplanted valve reconstruction. In patients with very heavily calcified valves or predominant (or pure) aortic regurgitation, the immediate results are clearly superior, and in all patients the data confirm the excellent clinical and hemodynamic results of valve replacement. However, they suggest that late embolism is a significant threat (incidence in the range of 20%). In addition, three patients have required and survived reoperation to correct persistent regurgitation with an associated hemolytic anemia.

Side Effects of Diastolic Augmentation on Renal, Carotid, and Femoral Blood Flow (P)

J. Schaefer, H. J. Schwarzkopf, W. Niedermayer, K. Held, and F. Ulmer, Kiel, Germany

The desired effects of appropriately timed diastolic augmentation are an increase in coronary blood flow (CF) and a decrease in tension-time index (TTI). However, side effects on flow in other vascular areas may be anticipated in view of the reversed arterial pressure configuration which develops during counterpulsation. Therefore, an investigation was carried out to determine to what extent arterial counterpulsation may alter blood flood to various organs. In 16 dogs flow measurements in the femoral (FA), the carotid (CA), the renal (RA), and the coronary arteries and the ascending aorta were obtained with a sine-wave electromagnetic flowmeter during diastolic augmentation. An average increase of about 10 to 20% in CF was observed, while cardiac systolic pressure and TTI were reduced to about 70%. With stroke volume and cardiac output remaining essentially unchanged, there was a marked decrease in FA and RA blood flow, accompanied by the appearance of a Venturi effect in the pressure tracing. This diminished flow in the vascular regions adjacent to the lower aorta may be caused by the suction of the counterpulsation apparatus during systole, which also could account for the observed shift in the baseline of the aortic flow curve. Whereas total CA flow stayed constant, there was a substantial increase in diastolic inflow, conforming to the altered pressure configuration.

Precipitating Factors in Acute Myocardial Infarction

Eric A. Schenk,‡ Rochester, New York

A study was undertaken to determine (1) the frequency of coronary artery thrombosis and degree of coronary artery sclerosis in patients with acute myocardial infarction (AMI), (2) the frequency of certain antecedent associated noncoronary factors influencing cardiac supply and demand in patients with AMI, and (3) the relationship between the status of the coronary arteries (CA) and the presence of these noncoronary factors. Of 3,203 sequential adult autopsies surveyed, 527 had died within ten days of an AMI and were included in this study. Seventy per cent of these had severe, 20% had moderate, and 10% had slight or no CA atherosclerosis. Recent thrombosis of a CA was found in 48%. Of the 527 patients with AMI, 14% had pneumonia, 12% had pulmonary thromboemboli, 16% had hypotension (postoperative, septicemic, or hemorrhagic), and 14% had diabetes. The incidence of these factors in patients with AMI was at least twice (and in the case of diabetes threefold) as great in patients without CA thrombosis as in those with CA thrombosis. The incidence of these factors, except for diabetes, was also significantly greater in patients with slight or moderate CA atherosclerosis than in those with severe CA atherosclerosis. These data show that (1) a number of noncoronary artery factors which might be implicated in affecting the supply and demand of the heart occur frequently in patients with AMI, and (2) these factors occur with a higher frequency in patients without CA thrombosis and without severe CA atherosclerosis, a group in which the reasons for the occurrence of myocardial infarction have always constituted a particularly perplexing problem.

Natural History of Homologous and Autologous Vein Grafts Used for Arterial Repair

Eric A. Schenk,‡ Hendrick B. Barner, and James DeWeese, Rochester, New York

The present report deals with an investigation of the morphological changes which occur in homologous (HVG) and autologous (AVG) saphenous vein grafts inserted into the femoral artery of the dog. Twenty-five HVG and 30 AVG were available and examined from five to 205 days after insertion. Eight of the AVG and ten of the HVG were thrombosed. Thrombosed grafts examined later than 30 days after insertion showed only organizing and organized thrombi with one exception; this was an acute thrombus in a HVG examined 70 days after insertion. Morphological changes found in all of HVG and AVG which were patent consisted of focal mural thrombi, intimal thickening due to smooth muscle and connective tissue proliferation, and medial degeneration and fibrosis. Evidence of an immune reaction characterized by necrosis and plasma cell infiltration was seen only in HVG examined from

20 to 45 days after insertion. This was always confined to the media and was variable in extent. HVG and AVG older than 60 days were entirely similar in appearance and could not be differentiated morphologically. The results indicate that (1) thrombosis in both types of grafts usually occurs within the first 30 days; (2) both types of grafts develop intimal proliferation and thickening and medial degeneration and fibrosis; (3) an immune reaction in HVG is confined to the media and may be related to the degree of medial fibrosis which has developed at the time of the immune response; and (4) the intimal thickening and medial fibrosis are most likely due to proliferation of host rather than donor cells.

Triglyceride Metabolism in the Isolated Perfused Rat Heart (P)

James Scheuer and Robert E. Olson, Pittsburgh, Pennsylvania

The purpose of this investigation was to study the metabolism of exogenous triglycerides (TG) by the heart. TG and palmitate appropriately labeled with C^{14} or H^3, either in the glycerol or fatty acid (FA) moiety, were administered intragastrically to rats, the chyle collected, and chylomicrons purified. The hearts of fasted rats were perfused with chylomicron suspensions for 30 minutes in a closed recirculating system. $C^{14}O_2$ was trapped in Hyamine. Heart lipids were extracted and separated on thin layer plates. Water-soluble extracts were analyzed for free glycerol or glycerol-C^{14}. Recoveries were expressed as micromolar equivalents of FA metabolized/g wet wt/hr. Palmitate-C^{14} TG was perfused at a concentration of 45.6 mg%. Myocardial recovery was phospholipid (PL) 1.1 μM, TG 5.2 μM, and FFA 0.2 μM. $C^{14}O_2$ recovery was 4.2 μM. Glycerol-C^{14} TG was perfused at a concentration of 51.0 mg%. Myocardial recovery was PL 0.1 and TG 2.5 μM. $C^{14}O_2$ recovery was 0.3 μM, and perfusate glycerol was 12.2 μM. Perfusion with glycerol-C^{14}-palmitate-H^3-TG (56.3 mg%) yielded recoveries comparable with single label experiments. Perfusate TG and myocardial TG C^{14}/H^3 ratios were 0.132 and 0.081, respectively. Hearts perfused five minutes had higher myocardial TG C^{14}/H^3 ratios than did hearts perfused 15 minutes. In all experiments the percentage of TG in the perfusate declined, and the percentage of mono- and diglyceride and free fatty acid (FFA) increased. The rat heart did not extract or metabolize free glycerol-C^{14}. The results indicate that intact neutral glycerides can be extracted and incorporated into the perfused rat heart. In addition, FA is released from the chylomicron, most likely by cell membrane lipoprotein lipase action, and then metabolized in the usual manner for FFA.

Sodium/Potassium Ratio in Myocardial Biopsies (P)

George Schimert, Oliver R. Hunt, Jr., James C. Brennan, and Mark Lillenstein, Buffalo, New York

Unsatisfactory replacement of potassium prior to open-heart surgery is detrimental to patients. Sodium and potassium determinations of papillary, atrial, and skeletal muscle obtained during mitral valve replacement were compared with determinations of similar specimens taken from autopsies and general surgical patients without potassium abnormalities. At the time of biopsy, arterial pH and serum potassium were also measured. The biopsies were homogenized and centrifuged with nitric acid, and the supernatant was read on a flame photometer using lithium water as an internal standard. The results were converted into mEq/kg of wet tissue. The average value determined for the various tissues of the same patients were skeletal muscle Na 63.61, K 102.55; atrial wall Na 118.41, K 62.30; and papillary muscle Na 99.17, K 76.92. The values of the control series reflected established normal ranges. The Na/K ratios were also determined and provided statistically high levels of significance.

These findings show a decreased potassium and increased sodium content in the myocardial biopsies taken during mitral valve replacement, as compared with autopsy and general surgical controls. If the method of tissue electrolyte analysis and the Na/K ratio truly express the intracellular distribution of sodium and potassium ions, these findings show intracellular depletion of potassium with a shift of the sodium into the cells. Total body water and electrolyte determinations, utilizing isotope dilution methods, are now added to the tissue analyses to investigate the ion shifts.

Effect of Fluorohydrocortisone on Forearm Vascular Responses to Norepinephrine

Phillip G. Schmid, John W. Eckstein, and Francois M. Abboud, Iowa City, Iowa

It has not been established clearly that mineralocorticoids increase vascular responsiveness to constrictor stimuli. The present experiments were designed to study in a systematic fashion the effects of chronically administered 9-alpha-fluorohydrocortisone on vascular responses to graded doses of norepinephrine.

Observations on forearm blood flow (plethysmograph), arterial pressure (cuff), and heart rate were made on eight healthy young men before and during four-minute intravenous infusions of norepinephrine bitartrate in doses of 0.075, 0.15, and 0.30 μg of base/kg/min. Each subject was

studied during three sessions. Experimental observations were made after administration of 9-alpha-fluorohydrocortisone, 1 mg initially and 0.2 mg daily, for seven days (session B). These observations were compared with control observations made before starting (session A) and three weeks after stopping (session C) the drug.

Blood flow averaged 3.2, 2.8, and 2.5 ml/min/100 ml of forearm, respectively, at the low, middle, and high doses of norepinephrine in session B. Corresponding averages were 3.3, 3.2, and 3.4 in session A and 3.4, 3.6, and 3.6 in session C. Decreases in flow were greater in session B ($P < 0.01$). Increases in mean arterial pressure, as well as decreases in heart rate, with increasing doses of norepinephrine were similar in each session. Increases in forearm vascular resistance were greater in session B than in sessions A or C ($P < 0.01$).

Greater increases in resistance in session B suggest that 9-alpha-fluorohydrocortisone increases responsiveness of vascular smooth muscle to norepinephrine.

Blood Velocity Profile Studies as Related to Atherogenesis

Daniel J. Schneck, William H. Gutstein, and Leon Bennett, New York, New York

The study of velocity profiles of flowing human blood in vitro under conditions of steady state has been undertaken in order to investigate the capacity of certain hemodynamic forces for injuring the vascular wall. A cineradiographic technique was employed by means of which time-displacement data were recorded. Neutral buoyancy, radiopaque pellets acted as tracers in order to determine local stream velocity. The velocity was then plotted as a function of distance from the tube wall in order to obtain the appropriate velocity profile under specified test conditions. Resulting profiles indicated that blood showed pseudoplastic behavior, even in tubes with diameters as large as 1 cm; that the degree of pseudoplasticity increased with decreasing tube diameter, becoming more evident in tubes approximating the size of the coronary arteries; that the degree of pseudoplasticity also increased with increasing flow rate, again becoming large at average rates comparable with those in the coronary arteries; and that the flow pattern of the blood was particularly sensitive to tube configuration. The increase in pseudoplasticity is associated with a rise in the shear stresses exerted by the blood against the lining of the vessels within which it flows. Microtrauma of the vascular lining as a direct result of these increased shear stresses is suggested as a possible mechanism for the development of spontaneous arteriosclerosis.

Lactate Metabolism in Low Flow States

William Schumer, Chicago, Illinois

The first part of this investigation provided evidence of a kinetic relationship between lactate production intracellularly (nonvital tissue) and plasma lactate after reinfusion of blood. Twenty-five dogs were bled to 25, 50, and 65% of their volume. At each bleeding increment biopsies were taken of the adductor magnus muscle, skin, and ileum. Lactate determinations were made on the homogenates, and it was found that as the volume bled was increased, there was an increase in lactate concentration intracellularly, particularly in the muscle, gastrointestinal mucosa, and smooth muscle cells. "Lactate pools" disappeared after reinfusion of blood, producing an increased plasma lactate and acidosis.

The second part of the study was undertaken in order to provide direct evidence incriminating lactic acidosis as the irreversible factor in low flow states. Thirty dogs were utilized. Polyethylene catheters were placed in the femoral artery and vein for bleeding and injection, respectively. Lateral flank incisions were performed from which the omentum was mobilized and placed on a microscope stage in order to visualize the microcirculation (150 to 645 × magnification). Twenty animals were bled 35% of their total blood volume. Ten animals were infused with lactic acid, 8 mM/L of total body water, causing the death of every animal; five animals were infused with sodium lactate, 8 mM/L of the total body water, with all animals surviving, and five animals were reinfused with blood and survived. The remaining ten animals were given lactate, 8 mM/L of total body water, without bleeding, and all succumbed. Microcirculatory studies of lactate infusion with and without 35% of total volume bled revealed findings similar to the state at 65% total volume bled; that is, increased cellular aggregation, pooling, and absence of flow.

Nuclear Histones as Controlling Factors in Cardiac Muscle Function

Arnold Schwartz, Richard A. Seibert, Wesley C. Starbuck, Charles W. Taylor, and Robert L. Vick, Houston, Texas

A factor isolated from the soluble fraction of heart muscle suspensions was shown to have been leached out of the nucleus during homogenization. The factor has now been identified as a histone-like protein with an amino acid content not dissimilar to that found in other tissues. Histone fractions, which have been obtained (F_1, F_2a, F_2b, F_3)

with variable contents of arginine, lysine, leucine, and isoleucine, were tested on the cardiovascular system. In low concentrations (10^{-11} to 10^{-8} M), the histones reversibly inhibited contractions of an isolated perfused rabbit heart and contractions of in situ guinea pig and cat hearts. Blood pressure recorded from the carotid artery of a rat seemed to change concomitantly with contractile changes in the heart. Electrical activity of the isolated heart in the presence of the histone showed alterations prior to the contractility changes, the most striking of which was a marked reduction of the T wave. Changes in the transmembrane potential of isolated Purkinje tissue of dog and cat heart have also been recorded. F_3 (an arginine-rich histone), e.g., in a concentration of 17 μg/ml, effected an increase in the rate of spontaneous discharge of the Purkinje fibers. These data were correlated with numerous studies at the enzymatic level showing inhibition or stimulation, depending on the ionic milieu (Ca to Mg ratio and ionic strength), of adenosine triphosphatases associated with various membrane-bound systems (mitochondria, sarcoplasmic reticulum, actomyosin) and suggest possible participation of basic nuclear proteins in cardiac function.

A Major Factor Limiting Gaseous Exchange in Membrane Oxygenators (P)

John Schwartz, Herbert J. Berman, Kevin Fallon, and James Halkett, Boston, Massachusetts

Millipore membrane 150 μ thick, rendered hydrophobic by a chemical process, retains its open interstices and surface porosity, thereby minimizing membrane resistance as a factor limiting gaseous exchange in a gas-membrane-blood system. This membrane was used to delineate other factors that limit exchange in membrane oxygenators. Rates of exchange of gases were determined in holders in which the thickness of the circulating blood layer was varied from 6 to less than 1 mm. The results were also expressed as a ratio, using a ¼ mil (6.35 μ)-thick Teflon membrane as the standard of comparison. Gas tensions were determined on a 160 Beckman gas analyzer.

The rate of elimination of CO_2 and addition of O_2 increased as the thickness of the blood layer decreased, but the ratios for Millipore to Teflon remained relatively constant, approximating 3 for CO_2 and 1.6 to 1.8 for O_2. Enhancement of the turnover of interface blood by intermittent compression of the membrane increased the ratio of CO_2 efflux to about 6. Under steady flow conditions, the ratio for a Dacron-backed Silastic membrane appreciably less than 5 mils thick to Teflon was about 1.5 for CO_2 efflux and 1.3 for O_2 influx.

These observations support the concept that the major limiting factor in exchange of gases in these membrane oxygenators is in the blood itself and not in the membrane, and that exchange is limited, possibly by laminar flow, to a very thin layer of blood against the membrane.

Contribution of Echocardiography to Clinical Cardiology (P)

Bernard L. Segal, William Likoff, and Benedict Kingsley, Philadelphia, Pennsylvania

Mobile echo signals from cardiac and vascular structures were recorded by a photographic "B: presentation and then by direct-writing phonocardiography with simultaneous electrocardiogram, phonocardiograms, and carotid pulses in 250 patients. Subjects comprised normal adults and patients with rheumatic valve disease, congenital heart disease, pericarditis, and abdominal aneurysm. The purpose was to determine ultrasound motion of the mitral and aortic valves, the anterior, septal, and posterior walls of the ventricles, and the aortic walls. Presentations were correlated with hemodynamic, selective angiocardiographic, and anatomical findings.

Slopes of mitral valve motion during diastole in normal subjects varied from 70 to 150 mm/sec. These were slower in mitral stenosis, varying from 35 to 40 mm/sec where the mitral valve area was greater than 1.5 cm^2 and 10 to 35 mm/sec where MVA was 1.2 cm^2 or less. Mitral regurgitation produced slopes of 170 to 190 mm/sec. In combined stenosis and regurgitation slopes were 40 to 60 mm/sec. Aortic valve motion was difficult to record, and slopes were not diagnostic. Ball-valve motion was recorded in aortic valve prostheses.

With cardiac enlargement the distance separating the echoes of the anterior, septal, and posterior walls varied from the normal values, depending on which chamber was enlarged. A cluster of echoes was noted beyond the posterior wall (pericardial sac) in patients with pericardial effusion. In abdominal aneurysms echoes identifying anterior and posterior walls were recorded.

Ultrasound recording from cardiac and vascular structures is a reliable, reproducible diagnostic procedure. These graphic presentations have been correlated with anatomical and pathophysiological findings.

Surgical Treatment of Mitral Insufficiency Following Myocardial Infarction

Arthur Selzer, John J. Kelly, Frank L. Gerbode, and William J. Kerth, San Francisco, California

Mitral insufficiency may occur as a sequel to myocardial infarction produced by rupture or

malfunction of a papillary muscle or by dilatation of the mitral ring. This report deals with surgical correction of this type of mitral insufficiency in four patients.

In selecting patients for surgical treatment, two criteria had to be fulfilled: (1) evidence of serious left ventricular failure and (2) evidence of gross mitral insufficiency. All four patients had physiological studies performed, which revealed low cardiac output, elevation of left atrial and pulmonary arterial pressures, and abnormal response to exercise. Angiocardiographic evidence of massive regurgitation through the mitral valve was obtained by retrograde left ventricular catheterization with injection of contrast medium into the left ventricle. The operation consisted of mitral valvuloplasty in two patients and of mitral valve replacement with a Starr-Edwards prosthetic valve in the other two. All patients survived the operation. Clinical follow-up and repeated hemodynamic studies revealed significant improvement in three patients; after initial improvement the fourth developed evidence of progressive myocardial insufficiency and died in cardiac failure several weeks after the operation.

On the basis of this study, it is concluded that (1) in carefully selected patients surgical correction of mitral insufficiency following myocardial infarction is a safe and useful method of treatment, provided gross mitral insufficiency exists; and (2) the presence of unrelated serious myocardial disease represents no contraindication for surgical correction of a mechanically overloading cardiac lesion.

Syndrome of Mitral Insufficiency due to Rupture of Chordae Tendineae

Arthur Selzer, M. Vannitamby, John J. Kelly, William J. Kerth, and Frank L. Gerbode, San Francisco, California

Examination of the mitral valve during open-heart operations has brought about a major conceptual reorientation of nonrheumatic mitral insufficiency. Within a few years mitral insufficiency due to rupture of chordae tendineae has changed from a pathological curiosity to an important and relatively common clinical syndrome. The purpose of this report is to describe clinical and hemodynamic features of this syndrome, based on 16 cases, and to report on surgical treatment of 14 patients.

The etiological factors included bacterial endocarditis in two cases, surgical damage from previous valvotomy in one rheumatic patient, and nonpenetrating trauma in one; other patients had no clinically or anatomically detectable causes, and rupture of the chordae was the only abnormality of the valve. In the majority there was a history of appearance of the murmur within a few years or months but without an acute illness in the intervening time. Clinical features revealed signs of pure mitral insufficiency; the presence of a systolic murmur in the aortic region correlated well with rupture of the chordae to the posterior leaflet of the mitral valve. Hemodynamic studies showed a wide spectrum of changes, varying from minor derangement of the circulatory dynamics to gross cardiac failure.

Surgical treatment consisted of a plication of the posterior mitral leaflet, uniting portions of leaflet with competent chordae, in seven patients in whom localized rupture of chordae was present. In three patients other plastic procedures were performed. In four patients multiple disruptions of chordae necessitated replacement with a Starr-Edwards prosthesis. There were one immediate and three late deaths; the clinical results vary from moderate improvement to almost complete cure.

Cardiac Disorders During Acute Emotional Stress

Herbert J. Semler, Portland, Oregon

Since opinions conflict as to the role of emotional factors in heart disease, we have investigated the influence of anxiety and tension on cardiac status in a subject's own environment uninhibited by medical supervision.

By means of portable, semiautomatic tape recorders, continuous electrocardiograms were obtained during spontaneous episodes of mental stress. The subject kept a diary, and symptoms were correlated with electrocardiographic changes by means of time-elapse clocks. A total of 452 continuous electrocardiograms of six to ten hours' duration were analyzed, with control observations in 163 normals compared with cardiac abnormalities in 289 patients.

In subjects with no evidence of cardiac disease, including negative exercise tests, only the electrocardiogram recorded under emotional stress documented the following: (1) Paroxysmal ventricular tachycardia of 22 seconds' duration appeared in a 16-year-old boy studying for a physics test. (2) Repetitive atrial flutter occurred in a 57-year-old contractor having palpitations five minutes after scolding his daughter. (3) A 41-year-old constable experienced substernal pain during an argument, accompanied by ischemic S-T segment depression; one week later he sustained an acute coronary occlusion. (4) While performing a sternal bone marrow aspiration, a 27-year-old physician's electrocardiogram showed pathological ST-T waves. (5) A 36-year-old school teacher noted "chest fluttering" during a crying episode, and electrocardiogram at the time demonstrated shifting supraventricular pacemaker with frequent ectopic beats.

Emotional stimuli can evoke cardiac symptoms with transient arrhythmias and ischemic electrocardiographic changes in clinically normal subjects. When anxiety accompanies cardiac disturbances, differentiation of myocardial disease from neurocirculatory asthenia can be facilitated by recording electrocardiograms at the instant symptoms occur.

Results of 110 Mammary Pedicle Operations for Angina Pectoris

William H. Sewell, Oteen, North Carolina

The pedicle operation has been done on 110 patients with severe coronary obstruction proven by selective coronary cinearteriography. The pedicle was placed under branches of the anterior descending and/or left marginal arteries.

The hospital mortality from all causes was three (2.9%) of the 104 patients in the good risk group, and it was five (83%) of six patients in the poor.

Selective mammary cinearteriography was attempted on 47 of the 48 patients who completed the first postoperative year. Technically adequate arteriograms were obtained on 45. Although the mammary artery was patent in 42, good filling of coronary arteries and preferably also of the coronary sinus from the mammary artery is believed necessary before the result can be considered satisfactory. There were no successful results in the five patients who did not have a coronary constriction to one-fourth normal or tighter in the vicinity of the pedicle. This much constriction was present in the other patients who had mammary arteriography. Successful arteriographic results were obtained in seven of the 15 patients who had the original type pedicle and in 21 of the 25 who had the revised version. Better clinical results are being obtained with the third version, but none of these patients has had mammary arteriography.

There were three (19%) deaths after the sixth postoperative month among the 16 patients who had proven failure of the pedicle. There were no deaths and no infarcts at any time among the 28 who had good mammary arteriographic results. There were no deaths or infarcts in the group of 24 patients who are between the sixth and twelfth postoperative months.

Neurological Syndromes Occurring in Patients on Synthetic Steroids (Oral Contraceptives) (P)

Sherif S. Shafey and Peritz Scheinberg, Miami, Florida

During the last year we have observed a host of neurological syndromes which developed in a group of females ranging in age between 20 and 39 years, all of whom were on some type of synthetic progestational medication.

The aim of this paper is to present the clinical and pathological material, discuss the possible pathogenesis, and make suggestions for future studies.

The clinical syndromes comprised the following: (1) Occlusive cerebral arterial disease with resultant cerebral infarctions—three cases had evidence of middle cerebral artery occlusion by arteriography. (2) Thrombosis of cortical veins and dural venous sinuses—one case was studied both clinically and pathologically at autopsy. (3) Pseudotumor cerebri—one case was studied clinically. (4) Migrainous-like and vascular headaches—ten cases which developed variants of the migraine syndrome after the institution of progestational synthetic steroids were relieved after discontinuing the drug.

A discussion of the pathogenesis includes the role of the hypercoagulable state which is produced by progestational steroids and the possibility of underlying vascular pathology in some of the patients.

It is felt that some of these complications can be avoided by proper choice of patients and awareness of the possible relationship between these vascular syndromes and the ingestion of progestational steroids. Our present opinion is that these drugs should be discontinued in the face of any symptoms suggesting vascular complications.

Dynamic Variation in Right Ventricular-Systemic Pressure Relationships in Tetralogy of Fallot (P)

Pravin M. Shah and Langford Kidd, Toronto, Ontario, Canada

Hemodynamic effects of isoproterenol, methoxamine, and amyl nitrite were studied in 11 patients with Fallot's tetralogy. The parameters observed included simultaneous pressures in central aorta (Ao), body of right ventricle (RV), and pulmonary artery (PA); oxygen consumption; O_2 contents in Ao, PA, and RV; first derivative (dp/dt) of RV pressure pulse; respiratory stethogram; phonocardiogram; and electrocardiogram.

Nine patients had a right-to-left shunt and two left-to-right under resting conditions. The Ao and RV peak systolic pressures were identical initially. Administration of isoproterenol and amyl nitrite inhalation increased the right-to-left shunt, while it decreased following administration of methoxamine.

The peak systolic pressures in Ao and RV decreased with amyl nitrite and increased with

methoxamine, the two remaining equal at all times. Isoproterenol infusion resulted in a decrease in Ao peak systolic pressure accompanied by an increase in RV systolic pressure in six of the 11 cases. A peak systolic gradient of 25 to 60 mm Hg (average 50 mm Hg) was noted. The other five cases did not demonstrate any gradient.

The dissociation between RV and Ao pressures reflects an isoproterenol-induced increase in resistance across the ventricular septal defect. This phenomenon was not observed after amyl nitrite, which also produced peripheral vasodilatation and an increased right-to-left shunt. It appears to be related to the positive inotropic action of isoproterenol. In conditions of increased endogenous catecholamine liberation (e.g. excitement, emotional stress, and exercise), it may occur spontaneously.

Hemodynamics of Complete Transposition of the Great Vessels Before and After Creation of an Atrial Septal Defect (P)

Reda M. Shaher and Langford Kidd, Toronto, Ontario, Canada

Pressures, hemoglobin, and oxygen saturations were measured and shunts and flows calculated in 19 patients with complete transposition of the great vessels before and after the creation of an atrial septal defect. Nine patients had a ventricular septal defect (VSD) (two with pulmonary stenosis), and ten had an intact ventricular septum. Of the group with a closed ventricular septum, the bidirectional shunt increased in eight and diminished in one; arterial O_2 saturation increased in nine and diminished in one; hemoglobin content decreased in seven and increased in two; systemic blood flow diminished in two, increased in five, and was unchanged in one; and pulmonary blood flow diminished in one and increased in one. Of those with a VSD, the shunt increased in four, diminished in one, and remained unchanged in four; arterial O_2 saturation increased in four, diminished in three, and was unchanged in two; hemoglobin content increased in four, diminished in four, and was unchanged in one; systemic blood flows increased in five and diminished in three; and pulmonary blood flow diminished in four.

It was concluded that (1) the procedure does not improve arterial oxygen saturation in any patient in whom it is 65% or more initially, (2) this operation is primarily of benefit when there is a closed ventricular septum, and (3) in those patients with a VSD, the operation does not prevent progressive pulmonary vascular obstruction.

Enhanced Human Cerebrovascular Responsiveness to Combined Hypoxia and Hypercapnia (P)

William Shapiro, Dallas, Texas, Albert J. Wasserman, and John L. Patterson, Jr., Richmond, Virginia

Simultaneous hypoxia and hypercapnia occur in cardiorespiratory failure. Each is a cerebral vasodilator, but their combined effects are largely unknown. Blood carbon dioxide tension (PCO_2) is of critical importance since moderate hypocapnia prevents dilatation due to hypoxia and maintenance of PCO_2 enhances this dilatation. The nitrous oxide (N_2O) technique was used to determine the cerebrovascular response to inhalation of 10% O_2 and 5% CO_2 in six normal volunteers. Mean changes from control were arterial PO_2 88 to 62 mm Hg; arterial PCO_2 38 to 44 mm Hg; jugular venous PO_2 34 to 38 mm Hg; cerebral blood flow (CBF) 56 to 97 ml/100 g/min; cerebrovascular resistance 1.7 to 1.1 mm Hg/ml/100 g/min; arterial pressure 96 to 107 mm Hg; minute ventilation ($\dot{V}$) 7.7 to 46.3 L; pulse rate 66 to 77/min (all $P < 0.01$). Since cerebral qO_2 was unchanged, the initial cerebrovascular responses were delineated by determining cerebral arteriovenous O_2 differences at ten one-minute intervals in six additional studies. Mean arterial and jugular venous PO_2 and PCO_2 and CBF equilibrated within two minutes, while $\dot{V}$ required five minutes. Mean CBF values during this period were lower than those observed after the prolonged inhalation necessary for the N_2O method. These two vasodilator stimuli produced more than a simple additive response because similar, separate alterations in either arterial PO_2 or PCO_2 would have produced no response or minimal response. This synergistic effect has important implications in interpretation of the pathophysiology of cardiorespiratory failure.

Effect of Phenoxybenzamine Hydrochloride on Pulmonary Blood Flow in Reimplanted Pulmonary Lobes

Akhila N. Sharma, Harry S. Soroff,† Andrew E. Bellas, and Ralph A. Deterling, Jr., Boston, Massachusetts

One of the chief problems encountered in the transplantation of pulmonary tissue is pulmonary vascular thrombosis. The purpose of this study was to evaluate the role of phenoxybenzamine hydrochloride (Dibenzyline) in preventing this complication.

Reimplantation of the left lower lobe was performed in an untreated group of 31 animals. Sev-

enteen of these animals died of pulmonary vascular thrombosis. Six animals died of other causes. Reimplantation was also performed in 12 animals who received 1 mg/kg of phenoxybenzamine for three days preoperatively and for five days postoperatively. The function of the left lower lobe was studied pre- and postoperatively by oxygen uptake, CO_2 release, diffusion capacity, left pulmonary artery pressure, and blood flow.

Six animals survived. The cause of death in one of the animals was pulmonary embolus. Two animals died of bronchial disruption, and two died of infection. Vascular thrombosis was not present in any of these animals. The survivors were studied between the thirtieth and the sixtieth postoperative days. The values for oxygen uptake, CO_2 release, and diffusion capacity were normal. Pulmonary artery pressure and cardiac output were not significantly changed in the immediate postoperative period. The pulmonary artery blood flow was not significantly reduced in the survivors and in the two animals who died of bronchial disruption, whereas it was reduced to 50% of the control values in the four animals who died of infection or on the first postoperative day.

It appears that pretreatment with phenoxybenzamine has reduced the incidence of vascular thrombosis following reimplantation.

Energy Equivalent Pressure and Extracorporeal Circulation (P)

Richard B. Shepard and Patricia A. Stinecipher, Birmingham, Alabama

An approach to identifying any specific value of pulsatile compared with steady flow for artificial hearts is to define quantitatively and compare energy content and spectral distribution in specific physiological situations. This study shows that the pulse wave does carry significant energy, in addition to that of mean flow and pressure, into the peripheral arterial tree and suggests that distal mean pressure gradients and perfusion are influenced by the kind of pulsatile flow. Total hemodynamic energy per ml of blood passing any given arterial site was calculated from phasic flow and pressure, expressed in mm Hg, providing an energy equivalent pressure. Studies were carried out in one patient and five dogs.

Energy equivalent pressure for steady flow is the same as mean pressure. For pulsatile flow it is greater than mean pressure. Energy equivalent pressure gradients along the arterial tree change with pulsatile flow, pressure waveforms, and phase relationships. These gradients are shown to be highly sensitive indicators of minimal obstruction and turbulence compared with mean pressure gradients. Energy equivalent pressure was higher in the aorta and carotid artery of dogs during self-perfusion than during extracorporeal perfusion. Energy equivalent pressures at the aortic root ranged from 5 to 30 mm higher than mean pressure. During the repair of an atrial septal defect, pulsatile flow energy was three times greater in the innominate artery during self-perfusion than during extracorporeal perfusion.

Energy equivalent pressure is a necessary concept in some pulsatile flow and perfusion problems.

Current Experience in the Diagnosis of Pheochromocytoma (P)

Sheldon G. Sheps, Gertrude M. Tyce, and Eunice V. Flock, Rochester, Minnesota

During the past five years urinary vanilmandelic acid (VMA) and metanephrines (MN) have been measured, in addition to plasma and urinary catecholamine (C) determinations and pharmacological tests, in 28 patients with pheochromocytoma. In 148 other patients this diagnosis was suspected but not confirmed by exploration (in 18) or by repeated study. Recently, pharmacological responses to tyramine and histamine have been compared.

Abnormal urinary valves were found in C in 21 of 28 tumor patients, for VMA in 22 of 27, and for MN in 13 of 14. In one patient all urinary values were normal. MN values revealed the greatest degree of abnormality in tumor patients. A positive result in the histamine test with an increase in plasma C was noted in 20 of 26 patients. A Regitine test was positive in ten of 26 patients, and the "basal" plasma C value was high in these ten. Tyramine tests in two tumor patients gave negative results, but results of repeated histamine tests were positive; plasma C increased only after administration of histamine.

Eight of 71 nontumor patients had positive results on histamine tests, and five of 44 had positive Regitine tests. Plasma C values were abnormal in two of 101. Among 201 24-hour urinary specimens analyzed, 40 had increased C content (six were more than twice normal), 18 had increased MN, and two had abnormal VMA. All MN and VMA values were less than twice normal; in no instance were both MN and VMA values increased.

MN and VMA were much less subject to false positive results than was urinary C, and since MN revealed the greatest change in tumor patients, it is our current screening test. However, either of the chemical or pharmacological tests occasionally may give a false negative result. Reliable diagnosis of pheochromocytoma still must be based on multiple studies in an appropriate clinical setting.

Failure to Confirm Pressor Effect of Corticosteroid Hormones in Treatment of Circulatory Shock

Herbert Shubin and Max H. Weil, Los Angeles, California

Corticosteroid hormones are highly effective in treatment of shock produced by injection of bacterial endotoxin in monkeys, dogs, rats, and mice. Recent data on patients with bacterial shock suggest that large doses of corticosteroids improve survival, and this effect is related to increase in cardiac output and lowering of arterial resistance. This "vasodilator" effect is incompatible with the hypothesis that corticosteroids exert their effect by potentiation of the pressor action of catecholamines, and in studies on normal subjects, no such effect was demonstrated. In the present study metaraminol or levarterenol was administered by infusion pump at a constant rate on 15 occasions to nine patients with circulatory shock due to bacteremia and other causes. Intra-arterial pressure, measured in the brachial or radial artery, was increased from 68 to 83 mm Hg. Cortisol or equivalent cortisone analogue was then administered in doses ranging from 0.25 to 2 g. In 11 of 15 studies, there was an average fall in intra-arterial pressure of 6.7 mm Hg (range 1 to 27, median 6) within the first two minutes. Arterial pressure returned to control values in the following 15 minutes. In three cases no change was observed, and in only one instance was arterial pressure increased. Clearly, the initial effect of the corticosteroid was vasodepressor ($P < 0.01$). Observations were continued for periods exceeding six hours, but no consistent change in arterial pressure was observed. We found no confirmation of the hypothesis that corticosteroid drugs in pharmacological doses potentiated the pressor action of levarterenol or metaraminol in patients with circulatory shock.

Studies of Strain Virulence of Group A Streptococci in a Pediatric Population (P)

Alan C. Siegel, Chicago, Illinois, Gene H. Stollerman, Memphis, Tennessee, Eloise E. Johnson, Chicago, Illinois, and Jorge T. Goobar, Cordoba, Argentina

Studies of a pediatric population have revealed the mildness of the streptococcal disease encountered from a clinical, immunological, and rheumatogenic standpoint. A systematic study of the strain virulence of the group A streptococci isolated from this population has been in progress during the past two years.

The streptococci were studied for properties which are known to be related to the amount of M protein and hyaluronic acid capsules produced, including (1) typeability and a semiquantitative estimate of M protein, (2) colony morphology, (3) capsule size, (4) chain length, (5) mouse virulence, and (6) resistance to phagocytosis in vitro.

Two hundred eighty-six strains of group A streptococci were studied, of which only 126 were typeable with M protein. The majority (94) of these typeable strains had a very low titer of extractable M protein. Thirty-five strains produced mucoid colonies, whereas 251 were glossy. Capsules were entirely lacking in 209 of the 286 strains; small capsules were present in 73, and only four had large capsules. Of 173 strains studied for mouse virulence, including all typeable strains, 82 were not virulent, 84 were slightly virulent, and only seven killed mice in doses of 1,000 organisms or less intraperitoneally. Only 33 of the 171 strains studied, including all typeable strains, resisted phagocytosis or grew well in human blood.

The majority of strains isolated, therefore, were of relatively low virulence and devoid of M protein and capsules. Those strains which possessed these substances were of a very low order of virulence and differed from those isolated during epidemics.

Effect of Vasopressors on Occult Myocardial Failure in Shock

John H. Siegel, Ann Arbor, Michigan, Edmund H. Sonnenblick, Bethesda, Maryland, Richard D. Judge, and William S. Wilson, Ann Arbor, Michigan

Among the causes of refractory hypotension is unrecognized myocardial failure secondary to diffuse myocardial disease when the heart has been further depressed by anoxia, anesthesia, or endotoxin toxicity. With the quantification of myocardial contractility provided by the isometric time-tension index, the present study in dogs demonstrated that when the myocardium is depressed, a vasopressor agent without cardiac inotropic activity may produce cardiac failure, even though increased arterial blood pressure and coronary flow result. However, vasopressors with inotropic action enable the depressed myocardium to compensate for the increased load imposed by peripheral vasoconstriction. The relative merits of methoxamine, angiotensin, and *l*-norepinephrine were compared. Methoxamine had a negligible inotropic effect and could force the occultly failing heart into overt hemodynamic failure. Angiotensin, while possessing a weak inotropic effect, also had a coronary vasoconstrictor action which might be hazardous to the already depressed myocardium. All of the vasoconstrictor agents studied produced evidence of reflex withdrawal of cardiac sympathetic activity. Only *l*-norepinephrine had a

sufficiently powerful inotropic action at therapeutic doses to give consistent protection to the depressed myocardium against the effects of its own vasopressor action. These studies suggest that if a vasopressor agent is to be used in the therapy of shock, when myocardial failure may be occult, it should have inotropic as well as vasoconstrictor effects.

Anatomical Evidence for Spontaneous Closure of Ventricular Septal Defect (P)

Robert L. Simmons, James H. Moller, Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

During a four-year experience with 1,605 necropsies of patients of all ages, seven cases with evidence of spontaneously closed ventricular septal defects were observed (about one per 225 cases). Each case involved an adult in whom no history of ventricular septal defect had been elicited.

In each case the defect was solitary. In six the defect was of the muscular variety, and in five of these it was located at about the midportion of the septum. Grossly, it was represented by a cleftlike depression between two distinct muscle bundles presenting on the left ventricular side. The base of the depression lay on the right side of the septum and in each case was closed by a plug of dense fibrous tissue.

The sixth muscular defect was located in the basal one-third of the septum. This defect, as well as the one case of "membranous" ventricular septal defect, was closed by adhesion of the septal leaflet of the tricuspid valve to the region of the right ventricular ostium of the defect.

No evidence of either active inflammation or myocardial infarction was present in relation to any of the defects.

Epidemic Nephritis in Trinidad

N. M. Simon, E. V. Potter, Chicago, Illinois, T. Poon-King, I. Mohammed, R. Cox, San Fernando, Trinidad, and D. P. Earle, Chicago, Illinois

An epidemic of acute glomerulonephritis started in Trinidad in September, 1964, the third since 1950, and reached its peak during January-February, 1965. By March, when the present pilot study was undertaken, 298 patients, 228 under ten years of age, had been admitted to San Fernando General Hospital from southern Trinidad and 150 to another hospital serving the northern portion of the island. Few patients had given a history of sore throat, but many had had infected skin lesions, impetiginous in character, for one to four weeks before admission.

Beta hemolytic streptococci were isolated from 15 of 21 patients admitted during the six days of this study (from skin lesions in 14 and from the throat in eight). Streptococci also were isolated from four follow-up patients, one mother, 30 of 50 normal school children in an area with nephritis, and 22 of 50 school children in an area without nephritis. Of 34 strains studied to date, 20 are group A, type 41.

During the same period 41 patients were observed in the hospital. Edema and proteinuria were found in 38, hematuria in 30, hypertension in 28, and increased blood urea in 23 of 33. Antistreptolysin O titers were increased in 66% (27 of 41).

The distinguishing features of the Trinidad epidemic were (1) its magnitude, (2) high incidence of impetiginous skin lesions, and (3) presence of a type of streptococcus not usually associated with acute glomerulonephritis.

Latent Pacemaker Activity as a Cause of Conduction Disturbances

Donald H. Singer, Ralph Lazzara, and Brian F. Hoffman, New York, New York

Impulse propagation is related to the level of membrane potential. Although conduction disturbances due to decreased membrane potential are usually associated with spread through incompletely repolarized fibers, the decrease in membrane potential resulting from slow diastolic depolarization in latent pacemaker fibers could cause similar disturbances.

To test this possibility, phase 4 depolarization was permitted to develop in strands of canine Purkinje fibers by gradually decreasing the frequency of stimulation. Transmembrane potentials were recorded from both ends of the fiber. The action potential upstrokes were electronically differentiated. The development of phase 4 depolarization caused conduction disturbances, ranging from simple slowing to decrement, local block, and changes in the sequence of activation of the fiber. The magnitude of change was dependent on the amount of depolarization. Suppression of phase 4 depolarization, by increasing the driving rate or cooling, and increasing membrane potential by hyperpolarizing stimuli or epinephrine usually reversed the changes.

Since latent pacemaker activity is common in Purkinje fibers, impulse propagation into these partially depolarized cells may be an important cause of conduction disturbances in the heart, including such difficult-to-explain phenomena as bundle-branch block occurring in association with slow heart rates, as well as exit and entrance blocks occurring about parasystolic foci. Observations that extrasystoles elicited during early diastole exhibited a greater amplitude and rising

velocity than those elicited late in diastole when phase 4 depolarization was more advanced suggest that this may also be a cause of "supernormal" conduction.

Social Status, Physical Activity, and Coronary Proneness

James S. Skinner, Washington, District of Columbia, Herbert Benson, Bethesda, Maryland, John R. McDonough, Washington, District of Columbia, and Curtis G. Hames, Claxton, Georgia

In a 1960–1962 survey of coronary heart disease (CHD) prevalence in Evans County, Georgia, it was found that high social class white males (HSC-WM) had significantly more CHD than low social class white males (LSC-WM) and Negro males (NM); little difference was found between LSC-WM and NM. Differences were inversely associated with amount of occupational physical activity engaged in. The purpose of this study was to determine activity patterns and physical working capacity in a random sample of this population. Physical activity was estimated by an activity questionnaire which objectively scored energy requirements of various activities. Physiological responses to increasing work loads were measured with a modified Balke treadmill test. Of 94 men aged 40 to 59 years, 32 were not exercised, and eight were terminated for medical reasons; 54 completed the treadmill test. No important differences were found between those exercised and not exercised or between those studied and the original population for height, weight, blood pressure, or cholesterol. There was little difference in mean pulse rate response to exercise among 17 LSC-WM, 18 HSC-WM, and 19 NM. HSC-WM were significantly less active in daily and occupational activity than LSC-WM or NM, who were very similar. An estimated difference in daily activity of 416 calories is similar to a difference in dietary intake of 196 calories found previously. To the extent that physical activity has a protective effect on CHD, this study may afford some insight into the amount of daily activity required to be beneficial.

Optimal Pulse Duration and Energy Threshold for Right Ventricular Endocardial Stimulation as Related to Power Pack Energy Consumption

Herbert Sklar, Doris J. W. Escher, Seymour Furman, and John B. Schwedel, New York, New York

Twenty heart block patients were paced for 31 studies through transvenous right ventricular bipolar electrode catheters (United States Catheter and Instrument Company no. C51, C52) by square wave stimuli of 0.01- to 5.0-msec duration with the negative pole first distal (DP-) and then proximal (PP-). Energy threshold was lowest with DP- in 18 and with PP- in 13 instances. At most sensitive polarity minimum threshold was at 2 msec in two and 1 msec (14) or below (0.5 msec in eight, 0.2 msec in seven) in 29 studies. The 14 studies optimal at 1 msec required an average of 4.3 ma (1.3 to 17.0), 2.1 v (0.6 to 8.0) at 518 ohms (300 to 833), or 16.2 microjoules (0.8 to 136).

In these 14 and in 13 of the remaining 17 studies, 55% more microjoules were required at 2 msec than at 1 msec at the same ohms, with insignificant changes in ma and v. All of these patients had originally paced at under 1.5 ma but shifted their requirements with shifts in catheter positions. Once stably positioned, energy requirement remained unchanged over days to years of continued pacing. Energy consumption in 16 of 20 unipolar studies was minimized by maintaining negativity at the optimum pole found in bipolar studies.

Since all patients who could be paced at 2 msec without exceeding the capacity of their usual pacemakers could also be paced at 1 msec, halving standard pulse duration to 1 msec would halve total battery drain without sacrificing the safety of patients.

Surgical Revascularization of the Heart (P)

Rodney T. Smith, Jack A. Cannon, Peter G. Gaal, and James A. McEachen, Los Angeles, California

Selective cinearteriography for the diagnosis of coronary artery disease has been used to select patients for myocardial revascularization procedures in 33% (20 out of 60) of the patients studied. During the past three years 18 patients have had endarterectomy, vein patch graft, or internal mammary artery implantation. Four operative deaths have occurred. Five patients restudied after one year show myocardial revascularization.

Arteriographic studies have shown several distinct anatomical patterns of disease. No single surgical approach can be applied to all of these variations. Certain patients may be treated by employing any one of the above-mentioned procedures, but others may require a combined approach.

The three most frequently encountered operable disease patterns include (1) obstruction within the proximal two-thirds of the right main artery, (2) obstruction of the origin of the anterior descending or circumflex arteries, and (3) left-sided small vessel disease.

Systolic Hypertension: A Presenting Finding in the Hyperkinetic Heart Syndrome (P)

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The idiopathic hyperkinetic heart syndrome may present with systolic ejection murmurs, electrocardiographic evidence of ventricular overload, and hyperactivity of the heart or great vessels. This report emphasizes the importance of systolic hypertension in the early recognition of this syndrome and describes the hemodynamic alterations observed with increasing work loads.

Sixteen patients who were referred to this center in 1964 for a diagnostic evaluation of systolic hypertension were found to have the hyperkinetic heart syndrome. Left- and right-heart catheterization and dye-dilution cardiac output studies were performed. During right-heart catheterization the patients were subjected to 50, 100, and 150 ergs of work on a bicycle ergometer.

Intra-arterial pressures in the brachial artery ranged from 148 to 194 mm Hg systolic. Left ventricular ejection rate ranged from 238 to 451 ml/sec/m^2. Cardiac output at rest was elevated in all patients. The highest recorded output was 11.2 L/min. During the work loads cardiac output increased an average of 5.5 to 6.0 L/min. Left ventricular ejection rate showed a similar rise. Intra-arterial diastolic pressures, which were all normal at rest, ranged from normal values to 120 mm Hg at maximum work loads.

Family histories revealed that "essential hypertension" was present in at least one parent in all but one case.

Our results suggest that systolic hypertension is a frequent presenting sign in the hyperkinetic heart syndrome. This syndrome should be suspected in all young patients with systolic blood pressure elevations. It is conceivable that these patients represent a prehypertensive clinical category, found in certain subjects who later develop "essential hypertension."

Intracardiac Electrocardiography and Pressure Recording at the Bedside with Hypertonic Saline

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Conventional methods for recording arrhythmias have limitations, particularly in the evaluation of atrial activity. This problem imposes diagnostic restrictions; in the monitored patient sequential rhythm changes may not be interpretable without precise definition of atrial activity.

Percutaneous insertion of an intravenous polyethylene catheter into the right atrium is a simple bedside technique accomplished without fluoroscopy or wires. Technically excellent intracardiac electrocardiograms were obtained through the catheter with 5% sodium chloride as the conducting medium, using the exploring lead of a standard electrocardiograph. Atrial wave contour provides a reliable, safe method for positioning the catheter.

The system permits simultaneous recording of central venous or intracardiac pressure, provides a central venous route of administration for therapeutic or diagnostic agents (i.e., indocyanine-green), and can serve as an intracardiac pacer under certain circumstances.

Twenty-five patients have been studied and monitored intermittently for as long as one week. In ten, resolution of a supraventricular tachycardia into atrial flutter, tachycardia, or fibrillation was possible. The monitoring of patients undergoing elective cardioversion has provided precise information regarding the exact rhythm prior to and following conversion. Intracavitary electrocardiograms have been obtained from the right and left heart in 15 additional patients at catheterization, using standard catheters in a similar fashion.

This approach may be used routinely for patients with rhythm disturbances and is more comfortable than esophageal electrocardiography, particularly in patients with fresh myocardial infarcts. Since a variety of parameters may be measured, its use is suggested as an ideal adjunct to monitoring patients with serious cardiac diseases.

Fructose and Free Fatty Acids After Fructose Loading in the Normal

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An excess intake of sugar has been suggested as a cause for the increased incidence of ischemic heart disease. Such a relationship could be due to a rise in the glyceride fraction of the serum lipids provoked by sucrose but not by other carbohydrates (starch, glucose). The glyceride response, in turn, could be due to a free fatty acid (FFA) response to fructose which is different from that to glucose. We therefore measured the FFA response to fructose in the normal and compared this with the FFA response to glucose in the normal. Fructose, glucose, and FFA were measured in six normals after 100 g of fructose and in 17 normals after 100 g of glucose perorally, and then the studies were carried out for five hours thereafter. The blood fructose level rose to a maximum at one hour and then fell exponentially to the fasting level at five hours. After glucose loading the FFA fell promptly to less than 200 mEq/L at one hour, remained stationary for two

more hours, and then rose briskly until the end of the test. In all but one of the fructose studies, the FFA failed to reach 200 mEq at one hour, continued to fall and to reach the nadir at between two and three hours, and then rose but did not reach the fasting level at five hours.

The FFA response to fructose is different from that to glucose. One possible cause for the difference is the lack, after fructose loading, of prompt, adequate insulin stimulation and its restraining influence on lipolysis.

Importance of Angiographic Assessment of the Coronary Arteries in Patients with Valvular Heart Disease

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Previous experience with three patients whose asymptomatic coronary artery disease was not evaluated by coronary arteriography and went unrecognized until operation for associated valvular or congenital heart disease has dramatized the importance of the angiographic assessment of the coronary artery tree in such patients. Two of these patients were premenopausal females, and the third was a male whose diffuse coronary sclerosis was severe enough to preclude adequate coronary perfusion during cardiopulmonary bypass.

Among 113 patients whose coronary arteries were evaluated angiographically, predominantly by the Sones selective cinetechnique or our modification thereof, 50 had valvular heart disease. Of these, 12 had angina pectoris, and 12 had electrocardiograms suggesting old myocardial infarctions. Significant obstructive coronary atherosclerosis was demonstrated by coronary angiography in eight patients. Four had angina pectoris, and three had electrocardiograms suggesting old myocardial infarction. Of interest is the fact that one patient in this group underwent surgery for severe aortic valvular stenosis and noted persistence of her anginal syndrome postoperatively.

The findings in this study indicate the difficulty of identifying accurately or excluding severe coronary sclerosis by clinical evaluation alone when it is associated with significant valvular heart disease. Optimal management of such patients with determination of the risk of surgery, as well as the likelihood of benefit from surgery, requires the angiographic assessment of the coronary artery tree as part of the evaluation, especially in those in the fourth decade or older. As better surgical techniques for the alleviation of coronary insufficiency become available, appropriate combined operative procedures for selected candidates having both valvular and coronary disease will improve results.

"Velocity Staircase" in the Human Myocardium: Effect of Heart Rate on the Dynamics of Ventricular Force Development

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The relation between heart rate and force of myocardial contraction has been found to differ among mammalian species, but no information concerning this relationship in the human heart is available. The effects of heart rate on right ventricular contractile force were determined with a Walton-Brodie strain gauge arch in 12 patients at the time of corrective cardiac operations. Six patients had atrial septal defects, three ventricular septal defects, and three aortic valve disease. Heart rate was controlled by electrical stimulation of the right ventricle in ten and the right atrium in two. Ten patients were studied on cardiopulmonary bypass, and in two the circulation was intact. As heart rate was increased from 54 to 170/min, only minor changes in contractile force were observed (average -9 ± 6.5 SEM %), but the rate of force development increased strikingly (average $+42 \pm 10.0\%$), while time to peak force fell progressively (average $-31 \pm 3.9\%$). Similar results were noted in 12 papillary muscles removed from patients at the time of mitral valve replacement and studied at various rates in a myograph. Thus, human myocardium does not display the classic Bowditch staircase in which force increases as rate rises but does exhibit what is termed a "velocity staircase." These findings suggest that in man an increased heart rate improves the contractile state of the myocardium since it augments the intrinsic velocity of contraction and decreases the duration of the active state, although the actively developed force remains unchanged.

New Method of Assisting the Circulation by Synchronous, Regional, External Pressure Pulsation (P)

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A technique for reducing left ventricular pressure work and increasing cardiac output without invasion of the vascular system is described. By means of a specially developed, sectionalized, rigid pressure chamber, the pressure external of selected portions of the body is synchronously pulsated.

A series of 30 experiments was performed. The hindquarters of the animal were isolated from the remainder of the body by a seal, and this portion of the tank was filled with water. Pressure pulses were then applied synchronously with cardiac

systole and diastole. This procedure introduced a synchronous extramural pressure pulse which resulted in a reduction in aortic systolic pressure, an increase in aortic diastolic pressure, an increase in venous return to the heart, and an increase in cardiac output. This preparation has made possible the control of blood volume distribution.

The effects of static tank pressure on venous return, cardiac output, and aortic pressure were documented. The hemodynamic changes produced by synchronous pulsating tank pressures at three levels of ambient pressure were measured. Optimum effects were produced with a negative ambient of −50 mm Hg and a positive going pulse of 100 mm Hg.

The aortic systolic pressure and PTM values were reduced by 30%, while cardiac output was increased by as much as 45%. Coronary flow was increased by 35% and renal artery perfusion by approximately 20%. No demonstrable hemolysis was produced, and animals which were assisted repeatedly over a period of weeks showed no untoward effects.

Role of Norepinephrine Stores in Determining the Contractile State of Myocardium and Its Responsiveness to Glycosides and Norepinephrine (P)

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The influence of cardiac sympathetic nerves in regulating myocardial performance is well recognized, and cardiac norepinephrine stores have also been found to play a crucial role in the maintenance of the basic contractile properties of myocardium and in the mediation of the inotropic response to glycosides. In order to evaluate these problems critically, the contractile properties of papillary muscles obtained from 12 normal (N), eight chronic totally cardiac denervated, norepinephrine-depleted (D), and five acutely reserpinized (3 mg ip × 2 days), norepinephrine-depleted (R) cats were studied. Complete force-velocity and length-tension curves were recorded in each muscle. Maximum isotonic velocities of shortening (V_{max}) were not significantly different, averaging 1.23 ± 0.11 SEM (N), 1.39 ± 0.11 (D), and 1.37 ± 0.11 (R) muscle lengths per second. Similarly, no significant differences were noted in maximum isometric tension (P_0), which averaged 7.43 ± 0.90 g/mm^2 (N), 8.85 ± 0.95 (D), and 9.14 ± 0.46 (R), respectively. Following addition to the bath of strophanthidin (1.0 μ/ml), P_0 rose by averages of 2.53 ± 0.45 (N) and 2.74 ± 0.53 (D) but increased significantly less ($P < 0.01$) after reserpine pretreatment (0.64 ± 0.36). The response of P_0 to added norepinephrine (1×10^{-10} to 1×10^{-5} M) revealed supersensitivity of the denervated myocardium with a shift of the dose-response curve to the left, while the reserpinized muscles responded normally. In conclusion, norepinephrine depletion produced by denervation or reserpinization does not depress the basic contractile state of myocardium. Norepinephrine stores and neural integrity are not essential for glycoside responsiveness, but reserpine itself interferes with the action of these drugs. Norepinephrine depletion by chronic denervation results in supersensitivity of myocardium to norepinephrine, while depletion by short-term reserpinization does not.

Effects of Ethyl-α-p-chlorophenoxyisobutyrate (CPIB) on Endogenous Hyperglyceridemia (P)

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Five subjects with elevated plasma triglyceride (200 to 4,000 mg%) which persisted or became more marked on fat-free diet (carbohydrate-induced lipemia) were studied on a metabolic ward. When plasma lipid became stable during administration of placebo or no therapy and fat-free formula feeding, 2 g of CPIB-ester per day were begun. A decrease of plasma triglyceride (TG) averaging 50% occurred in all subjects within ten days. The turnover rate of isotopic TG glycerol in either less than 1.006 or less than 1.019 lipoprotein was determined before and 12 hours after CPIB-ester was begun, the latter before change in plasma concentration had been produced. The T½ was markedly shortened following the drug. These findings indicate that CPIB-ester is effective in hyperglyceridemia which is wholly endogenous, indicating a mechanism of action separate from the clearing of alimentary lipid. The change in glyceride glycerol kinetics suggests that the drug acts by increasing oxidation or removal of lipoprotein triglyceride rather than by affecting its synthesis rate.

Comparison of Vasopressors During Hypovolemic and Hyponatremic Shock in Dogs

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This paper is a continuation of a broad evaluation of certain vasopressors (angiotensin amide, epinephrine, metaraminol bitartrate, and norepinephrine) which has been in progress. Previous studies were concerned with monitoring renal and

aortic flows and sytsemic blood pressure during hypovolemic shock and during administration of the above-mentioned vasopressors. It was the purpose of this investigation to compare and duplicate similar recordings during hyponatremia with those standards arrived at previously.

The hyponatremic state was achieved by peritoneal dialysis, while hypovolemic shock was standardized by keeping the blood pressure at a mean of 50 mm Hg for 90 minutes. Vasopressors were then administered, while renal and ascending aortic flows were monitored with flowmeters. The degree of acidosis and the serum sodium and potassium levels were also followed. During hyponatremic shock the serum sodium values fell from around 140 mEq/L to around 115, and arterial pH dropped from 7.4 to 7.1. Similar decreases in pH were seen in the hypovolemic study. In the hypovolemic dogs the vasopressor which elevated renal flow the greatest was angiotensin (a 26% increase over control levels), while slight changes or decreases were noted with other agents (epinephrine decreased 4%). During normovolemic control studies only angiotensin consistently elevated renal flow, while other agents all decreased flow. During hyponatremic shock all vasopressors elevated renal flows (angiotensin 18%, epinephrine 11% increase over control levels, norepinephrine 23% increase over control levels, metaraminol 4%). These observations plus other data obtained, we believe, are evidence that some form of desensitization to vasopressors has occurred during hyponatremia.

Tricuspid Replacement: Clinical Experience with the Ball-Valve Prosthesis

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Tricuspid pathology is not infrequently encountered in the surgical treatment of mitral or combined mitral and aortic valve disease. The initial morbidity and mortality as well as the late results in such cases may depend on its proper management.

This report is based on experience with 19 tricuspid replacement procedures: 14 with single-stage triple replacement, one with two-stage triple replacement, and four with mitral replacement alone. Eleven patients had resection and replacement for combined tricuspid stenosis and regurgitation. Eight patients had resection and replacement for pure regurgitant lesions related to ventricular valvular disproportion without clear evidence of rheumatic involvement of the tricuspid valve. Relief of mitral disease in these patients did not result in improvement of tricuspid function, and replacement was required to restore adequate cardiac function.

Nine additional patients with significant tricuspid disease had commissurotomy, annuloplasty, or no treatment directed at the tricuspid valve.

Sixteen of the replacement group survived operation. There were two deaths in the nonresection group, and one patient required reoperation and subsequent replacement.

There were no complications due to tricuspid replacement, such as pulmonary embolus, heart block, or unusual rhythm disturbances. Serial cardiac output studies in the recovery room and late cardiac catheterization revealed superior cardiac performance of the replacement group compared with those with residual tricuspid disease.

Thus, tricuspid replacement is a safe adjunct to multiple valve surgery to be used in patients with significant tricuspid dysfunction not amenable to complete correction by reparative procedures.

Earliest Manifestations of Bacterial Endocarditis After Prosthetic Valve Implantation

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The implantation of prosthetic valves has afforded a unique opportunity to study the earliest clinical manifestations of bacterial endocarditis (BE). Seventeen of 288 patients developed BE following ball-valve implantation. Diagnosis was made on the basis of autopsy evidence in ten patients and on the basis of two or more positive blood cultures in seven surviving patients. In 15 patients fever was either continuous from the first postoperative day or delayed in onset up to 25 days after operation. Sites of infection predisposing to BE were present in 13 patients. In four, murmurs of prosthetic valve incompetence appeared. At the time of the first positive blood culture, eight patients looked sick, whereas six looked and felt well. Fever exceeded 102 F in 11, white blood cell count was above 10,000 in nine, hematuria had occurred in six, and episodes suggesting cerebral emboli had occurred in seven. Only one patient had petechiae. None revealed splenomegaly, splinter or conjunctival hemorrhages, or Osler nodes.

It is concluded that the major feature suggesting BE in patients with prosthetic valves is fever, especially when associated with foci of infection (e.g., wounds). The most important supportive findings were cerebral symptoms, hematuria, and prosthetic insufficiency murmurs. The usual confirmatory signs of BE were absent. Occasionally, patients looked well, the only finding being positive blood cultures and low-grade fever. The diagnostic importance of blood cultures in febrile patients after prosthetic valve implantation is emphasized.

Degeneration of Autogenous Vascular Grafts in Experimental Atherogenesis

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The technique for the development of reproducible canine experimental atherosclerosis has allowed a long-term comparison of numerous factors affecting deposition of atheromatous material. This study was undertaken to evaluate the relative advantage of three autogenous tissues for use as an abdominal aortic replacement.

Three groups of mongrel dogs were prepared and placed on an atherogenic diet previously described: (1) A segment of the abdominal aorta was dissected free, reversed, and resutured. (2) A segment of the pulmonary aorta was resected and replaced by an aortic autograft, and then the pulmonary artery segment was sutured into the abdominal aorta. (3) A segment of the abdominal aorta was isolated from the general circulation and the aortic defect bridged with a jugular vein graft. All the animals responded with satisfactory elevation of the serum cholesterol levels and were sacrificed at the completion of the study from six to 18 months after the dietary regimen was begun.

All autogenous tissues developed experimental atheroma. These lesions were not so severe, however, as previously reported lesions utilizing synthetic grafts. Group A (aortic) demonstrated fewer lesions than did the other two groups, but also a different type of deposit was noted in group A.

Unnatural History of Ventricular Septal Defects

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Since 1957, 345 patients have had open-heart surgery for the closure of ventricular septal defects at the University of Michigan Medical Center; 319 survived the operation. Forty-six patients were less than two years old. Thirty-one of the infant group had severe pulmonary hypertension, with pulmonary artery pressure greater than 75% of the systemic artery pressure. Twenty-one survived. No deaths occurred in the remaining 15 infants having lower pulmonary artery pressures. Of the 299 patients older than two years at the time of surgery, 255 had pulmonary artery pressures of less than 75% of systemic pressure. There were three surgical deaths in this group. Ten of the remaining 44 older patients with severe pulmonary hypertension died in association with surgery. The only two late deaths of the operated patients were unrelated to the heart.

Although spontaneous closure of the ventricular defect may occur, evidence thereof is generally present before two years. Only those patients in severe distress were offered surgical closure in infancy. If no predisposition to spontaneous closure was observed, surgery has been recommended, usually in the year prior to school. This recommendation is based on the expectation of preventing bacterial endocarditis, relief of the shunt load, and removal of the "fragile child" approach to life.

Results of a Cardiac Monitoring Unit in Treating Cardiac Arrest (P)

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This study relates a ten-month experience in cardiac resuscitation of a four-bed cardiac monitoring unit equipped with special nurses, resuscitation facilities, and continuous oscilloscopic electrocardiogram display. Cardiac arrests were divided into three categories according to the electrocardiogram when first observed following arrest: (1) absent or few ventricular complexes indicated electrical standstill; (2) ventricular complexes at rates between 40 and 120 without apparent cardiac muscular contraction indicated mechanical cardiac arrest; and (3) ventricular fibrillation. Successful resuscitation was deemed to have occurred if there was survival for 24 hours and consciousness was restored.

Twenty-eight patients (12% of 231 admissions) experienced 33 separate arrests following admission to the unit. Electrical standstill occurred in two patients. Both were successfully resuscitated, but only one still survives. Mechanical arrest occurred in 11 patients (33% of 33 total arrests), and there were no successful resuscitations in this group. Ventricular fibrillation took place 20 times (61% of 33 total arrests) in 15 patients. Successful resuscitation in 11 of 15 patients was possible in 15 of 20 (75%) episodes of ventricular fibrillation. Six of these 15 patients (40%) still survive, and five have been discharged from the hospital. The diagnoses in surviving patients included acute myocardial infarction, rheumatic heart disease, and congenital heart disease.

It is concluded that mechanical cardiac arrest cannot usually be treated successfully with present techniques. Successful resuscitation from ventricular fibrillation is possible in the majority of patients who are in a special cardiac monitoring facility.

Hypotension and Plasma Serotonin Levels in Dogs

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It is possible to demonstrate reliable recoveries of plasma serotonin of 92.5% ($\pm$ 5.8%), using a chemical extraction and the spectrophotofluoro-

metric method of Waalkes. Plasma serotonin levels were studied in nine adult mongrel dogs during periods of moderate to severe hypotension induced by hemorrhage. The dogs were anesthetized with thiopental sodium and then heparinized. Serial protamine titers were determined, and heparin was added as indicated to maintain protamine titers above 60 μg/ml. Control samples were drawn to determine normal plasma serotonin levels before subjecting dogs to one to two and one-half hours of hypotension at a mean arterial pressure of 50 mm Hg. Under the experimental conditions outlined above, normal peripheral plasma serotonin levels in nine dogs ranged from 0.007 to 0.020 μg/ml with a mean of 0.012 μg/ml. Plasma serotonin levels did not change during 60 to 150 minutes of hypotension at 50 mm Hg mean arterial pressure. When trimethaphan was used to achieve comparable levels of hypotension in seven dogs, there was likewise no change in plasma serotonin levels.

Clearance of Intramyocardial Radiokrypton as an Index of Regional Myocardial Blood Flow (P)

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Clearance of locally injected isotope has been used to measure blood flow in skeletal and cardiac muscle. Radiokrypton, dissolved in saline, was used to measure blood flow in the myocardium at open pericardiotomy in dogs and in human subjects with coronary artery disease. Sequential subepicardial injections were made at selected local sites in the myocardium with precordial scintillation monitoring of each regional clearance rate. In anesthetized, thoracotomized dogs clearances measured after injection down the left anterior descending artery through a fine indwelling catheter yielded values which were consistently 10% higher than clearances following adjacent intramyocardial injections. Repeated multiple site intramyocardial clearances were reproducible, indicating homogeneous flow in normal subepicardial myocardium. Clamping of the artery caused immediate cessation of intramyocardial clearance with immediate return on release of the clamp. Multiple regional clearances were measured in six patients with left anterior descending and left circumflex coronary artery disease undergoing internal mammary artery implantation. Marked zonal reduction of clearance, in reference to other areas, was detected, particularly distal to stenotic areas of the left anterior descending artery and in regions of evident tigroid scarring. Implantation sites of internal mammary pedicles were selected, in part, by such measurements to avoid scar and encompass areas of locally reduced blood flow. These measurements confirm the long suspected heterogeneity of myocardial flow in coronary artery disease.

Acute Hemodynamic Effects of Peritoneal Dialysis (P)

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In reviewing our experience with the last 100 patients undergoing peritoneal dialysis for uremia, acute pulmonary edema was noted in three instances and acute hypotension in three instances. The pulmonary edema improved on emptying the abdomen of peritoneal fluid. In view of these sudden unexpected changes in cardiovascular status during peritoneal dialysis, the acute hemodynamic effects of the infusion of 2 L of fluid into the peritoneal cavity were evaluated.

Ten patients were studied. Cardiac output (CO), intra-arterial blood pressure (BP), pulmonary artery pressure (PA), and central venous pressure (CVP) were measured before instillation of the peritoneal fluid, immediately thereafter, at the end of one hour of peritoneal fluid instillation, and after emptying the peritoneal cavity. All studies were done with the patient in the horizontal position and after elevating the head of the bed 30 to 40° from the horizontal. Cardiac output declined an average of 0.76 L/min (15%) immediately after the instillation of peritoneal dialysis fluid. Head-up tilting resulted in a further decrease of 0.380 L/min (10%). Intra-arterial pressure and pulse rate showed no significant change. Mean pulmonary artery pressure increased an average of 4 mm Hg (15%) on instillation of peritoneal dialysis fluid; this did not change with head-up tilting. Cardiac output returned to levels above control in both the horizontal and head-up position after emptying the peritoneal fluid from the abdomen. Pulmonary artery pressure returned to below control levels after emptying the abdomen.

The decrease in CO and increase in PA may be explained by a decrease in total venous return with displacement of blood from the systemic to pulmonary circuit.

Management of pulmonary edema occurring during peritoneal dialysis has best been accomplished by emptying the abdomen and refilling with a smaller volume of hypertonic dialysate.

Mechanism of Action of Cardiac Glycosides in Relation to Endogenous Cardiac Catecholamines (P)

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The following studies were performed to test the hypothesis that digitalis-induced augmentation

may be related to the presence of an increased level of cardiac catecholamines. Cat papillary muscle and Langendorff preparations were used to study the positive inotropic action of ouabain in the presence and absence of reserpine and guanethidine pretreatment. Ventricular catecholamine content of 15 controls was 1.63 μg/g (SE $\pm$ 0.122). Following reserpine (0.5 mg/kg/day $\times$ 3), the catecholamine content of 14 hearts was reduced to 0.0285 μg/g (SE $\pm$0.00196), and for 14 guanethidine-treated cats (15 mg/kg/day $\times$ 2), it was 0.14 μg/g (SE $\pm$0.0092). The ventricular catecholamine content in 11 animals after the administration of both reserpine and guanethidine was 0.0171 μg/g (SE $\pm$0.0017). The peak mean response following exposure to a toxic dose of ouabain (0.5 μg/ml), in terms of the percentage of initial contractile force for papillary muscles, was as follows: controls (eight) 213.9, reserpine (ten) 150.7, guanethidine (11) 135.9, and reserpine plus guanethidine (11) 158. Similarly, for the Langendorff preparations it was controls (11) 172, reserpine (12) 139.2, guanethidine (9) 141.9, and reserpine plus guanethidine (eight) 127.3. In all cases cardiac preparations from pretreated animals displayed a significantly smaller peak positive inotropic response than the ouabain controls. These data indicate that ouabain-induced augmentation is related, at least in part, to the increased release and/or availability of endogenous cardiac catecholamines.

Hemodynamic Studies in Natives of High Altitudes with Patent Ductus Arteriosus

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The clinical picture of patent ductus arteriosus (PDA) at high altitudes is different in several aspects from PDA at sea level, probably because of the effect of chronic hypoxia on the pulmonary circulation.

To study this hypothesis, right-heart catheterization was performed on 18 natives from Cerro de Pasco, Peru (14,200 feet above sea level) with PDA. The data were obtained while the patients were breathing room air and during oxygen administration.

With room air a pure left-to-right shunt was found in 14 patients and bidirectional shunts in four, with a mean pulmonary blood flow of 11 L/min/m^2. Calculated pulmonary resistances were similar to those of healthy residents from the same altitude. Pulmonary artery pressures (average 68/39, mean 54 mm Hg) were higher than in healthy natives, in whom a mild degree of pulmonary hypertension is a common finding (average of 25 observations: 41/18, mean 28); pulmonary pressures were also higher than in patients with PDA from sea level (average of 16 observations: 27/10, mean 17. During O_2 administration the following effects were observed: a marked increase in pulmonary blood flow, about 50% reduction in pulmonary resistance, and a moderate fall (about 35%) in mean pulmonary artery pressure.

The results suggest that the higher degree of pulmonary hypertension found in high altitude residents with PDA is related to an important degree of pulmonary vasoconstriction. The increased pulmonary blood flow and structural changes of the pulmonary vasculature similar to those reported in healthy residents are contributing factors.

Tricuspid Valvular Replacement: Experimental Study in Calves

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The Starr-Edwards prosthesis has been extensively employed for mitral valve replacement, but few clinical or experimental data are available concerning its use in the tricuspid position. The tricuspid valve was replaced with a 3M Starr-Edwards prosthesis in 35 calves weighing 58 to 81 kg. Standard valves were inserted in ten animals, and a valve coated with graphite-benzalkonium-heparin was utilized in 12. Thirteen additional animals with standard valves were given low molecular weight dextran for three days after operation and intramuscular warfarin daily thereafter.

The valves have been examined in 19 calves which died or were sacrificed postoperatively. Two graphite-coated valves were free of clot at one day and two months after insertion, two were totally obstructed by clot at one week and three and one-half weeks, and another had thrombus on the cage at four and one-half months. In each of seven calves not anticoagulated, the standard valve showed thrombus. Two died after one month and four months with complete obstruction; in five others thrombus was present on the cage at one day to six months, but the valve function appeared satisfactory. In six animals with standard valves given warfarin, no thrombus was present one day to six months after operation; one had organizing thrombus on the cage at five months, but warfarin administration had been interrupted in the week preceding sacrifice.

Continuous anticoagulation is apparently necessary after tricuspid valve replacement, but the 16 calves still alive will provide additional information about this hypothesis.

Effects of Octapressin and Vasopressin on the Vascular Resistance of the Mesenteric, Gastric, Splenic, and Renal Circulations

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The direct effects of octapressin (phenylalanine^2-lysine^8-vasopressin-PLV-2) and vasopressin on the mesenteric (M), gastric (G), splenic (S), and renal (R) vascular beds were studied by the constant flow perfusion technique. Isotonic solutions of PLV-2 (0.005 to 0.01 units/ml) and vasopressin (0.05 to 0.1 units/ml) were infused at sequentially increasing rates (0.1 to 4.8 ml/min) directly into the arterial circulation of 45 dogs. Total resistance (PRU) was determined for each vascular bed and, in addition, segmental resistance for the mesenteric circulation. At maximum infusion rates PLV-2 increased mean total vascular resistance, as compared with control values, for the mesenteric (MR_T) 54% ($P < 0.001$), gastric (GR_T) 32% ($P < 0.01$), splenic (SR_T) 44% ($P < 0.001$), renal (RR_T) 14% ($P < 0.2$), mesenteric small artery (MR_{SP}) 20% ($P < 0.02$), and mesenteric small vessel resistance (MR_{SV}) 86% ($P < 0.001$). Vasopressin increased MR_T 62% ($P < 0.001$), GR_T 29% ($P < 0.001$), SR_T 35% ($P < 0.005$), RR_T 20% ($P < 0.02$), and MR_{SA} 12% ($P < 0.2$). The corresponding increase in R_T for PLV-2 and vasopressin at 0.15 and 1.8 units/ml flow/min, respectively, were 54%, 22%, 14%, and 3% and 62%, 16%, 17%, and 9%. R_V was not changed by either agent. Both peptides increased vascular resistance of the mesenteric, splenic, and gastric circulations; renal vascular resistance was not affected by octapressin but was decreased by vasopressin.

Octapressin is the most potent constrictor of the splanchnic bed, having eight times the pressor potency of vasopressin. The unique vasoactive properties of octapressin suggest possible clinical use in gastrointestinal hemorrhage and hemorrhagic shock.

Comparative Hemodynamic Effects of Peripheral Vasoconstriction in Normal and Thyrotoxic Subjects (P)

Ernest O. Theilen and William R. Wilson, Iowa City, Iowa

These studies were done to determine whether the high cardiac output of thyrotoxicosis might be a reflex phenomenon secondary to peripheral vasodilatation. Phenylephrine (1.0 and 2.0 μg/kg/min iv) was given to seven normal subjects (group I) and seven thyrotoxic subjects (group II) after attenuation of its bradycardic effect (atropine 1.0 to 2.7 mg iv).

Before atropine average control systemic mean arterial pressures (SMAP) and mean right atrial pressures (MRAP) were similar in both groups, but heart rate (HR) of 107 and cardiac index (CI), determined by indicator-dilution, of 5.0 in group II were higher ($P < 0.01$) than in group I (69 beats/min; 3.3 L/min/m^2). After atropine SMAP (91, 107 mm Hg), MRAP (3.3, 4.1 mm Hg, HR (111, 129 beats/min), and CI (4.3, 4.8 L/min/m^2) in groups I and II, respectively, were insignificantly different.

Increases in SMAP with phenylephrine in group II (+36, +48 mm Hg) did not differ appreciably from group I (+32, +52). Similar increments in MRAP occurred in both groups. Reductions in HR in group II (−7, −4 beats/min) differed insignificantly from those in group I (−11, −18). Decrements in CI in group II (−1.0, −1.5 L/min/m^2) were much greater ($P < 0.05$) than in group I (−0.3, −0.1). Increments in resistance in group II (+868, +1,303 dyne/sec/cm^{-5}) were larger ($P < 0.05$) than in group I (+429, +672). Changes in stroke work index in group II (+0.59, −0.02 units) were less ($P < 0.05$) than in group I (+2.56, +4.42).

Peripheral vasoconstriction reduces the cardiac output of the hyperthyroid but not that of the normal subject when his baroreceptor reflexes are attenuated, suggesting that the high cardiac output is secondary to peripheral vasodilatation.

Myocardial Succino-Oxidase and Myosin Enzyme Activities During Coronary Arterial Infusion of Histamine in Dog

Janaki Bai Theogaraj, Young W. Cho, and Samuel Bellet, Philadelphia, Pennsylvania

The direct action of histamine was studied in dogs to evaluate the possibility of histamine being the primary amine to disrupt the integrity of cardiac mitochondrial functions, as well as the myocardial contractile proteins, during endotoxic or hemorrhagic shock.

The left coronary artery was catheterized via the left carotid artery, and histamine (10 to 15 μg/kg) was infused at constant rate for 15 minutes in reserpinized, bilaterally vagotomized dogs. The aortic blood flow rate (1.25 to 1.50 L/min) and the aortic blood pressure (110 to 140 mm Hg) were slightly increased within one minute of histamine infusion and persisted for five to ten minutes. The calculated LVWD was increased about twofold (1.315 to 2.702 kg-m/min/m^2) within one minute. There were no significant changes in the cardiac mitochondrial cytochrome oxidase (27.69 ± 16.34 to 23.14 ± 10.20; $P < 0.4$) and myosin adenosine triphosphatase (0.067 ± 0.0116 to 0.071 ± 0.0174 μM P_i/mg of protein/min; $P < 0.2$) of the dog with or without

the histamine infusion. The succinate dehydrogenase (0.3005 ± 0.08179 to 0.2213 ± 0.06542 per mg protein/min; $P < 0.01$) and mitochondrial adenosine triphosphatase activity (1.982 ± 0.5394 to 1.538 ± 0.4517 μM P_i/ml mitochondria/5 min; $P < 0.01$) were significantly decreased with histamine infusion. The studies suggest that histamine might be the primary chemical mediator to induce myocardial cellular parameter changes during shock or acute hypoxia. During the initial period of acute hemorrhage and acute hypoxia, arterial plasma histamine was increased.

Role of Platelets in Sudden Death Induced by Experimental Pulmonary Emboli

Duncan P. Thomas and Victor Gurewich, Boston, Massachusetts

Autologous thrombi were released into the lungs of anesthetized rabbits from their site of formation in the jugular veins. Blood samples for platelet counts were obtained by means of a catheter in the carotid artery immediately before and three minutes after release of the thrombi. Seven out of 30 embolized animals died in acute respiratory arrest within a minute of release. Another five animals showed marked slowing of respirations with labored breathing and periods of apnea but did not die. The remaining animals had only minor respiratory changes. By rank analysis a highly significant ($P < 0.01$) relationship was found between the number of circulating platelets before release of thrombi and ensuing sudden death or marked respiratory distress. The 12 animals dying or distressed following embolization had an average control platelet count of 589,000 per mm^3. The remaining 18 animals had an average count of only 345,000. The platelet count three minutes after embolization dropped by an average of 20%.

In dogs autologous thromboemboli induce acute bronchoconstriction by releasing serotonin from platelets. This release, induced by traces of thrombin on fresh pulmonary emboli, may be an important factor in causing sudden death. In man a correlation has been reported between postoperative and postpartum elevation of the platelet count and the development of clinically apparent thromboemboli. It is suggested that the severity of the clinical response to pulmonary emboli may well be directly related to the number of circulating platelets.

Hemodynamic Response to the Infusion of Isoproterenol in Dogs with Left-to-Right Shunts

Kenneth E. Thomas, Thomas D. Darby, and Herbert E. Warden, Morgantown, West Virginia

In normal dogs isoproterenol infusion produces early contraction of the right ventricular outflow tract (RVO), shortening of the baseline RVO muscle segment length (MSL), and a significant right ventricular (RV)-pulmonary artery (PA) pressure gradient. The hemodynamic effect of this drug in the presence of chronic left-to-right shunts was studied.

Atrial and ventricular septal defects were created in dogs. Four to 14 months postoperatively, pulmonary and systemic blood flows were determined with indicator-dilution techniques. Simultaneous RV and PA pressures were recorded, as well as RVO-MSL, with a modified Cushney gauge.

Control left-to-right shunts in 13 dogs averaged 54% of pulmonary blood flow, ranging between 34% and 72%. After isoproterenol infusion at 0.5 μg/kg/min, the left-to-right shunt decreased by 34%, with average mean systolic RV-PA gradients increasing from 7 to 16 mm Hg. In animals with mean systolic RV-PA gradients greater than 9 mm Hg, there was earlier contraction of the RVO than was observed in normal dogs. In response to isoproterenol, all dogs demonstrated early contraction of RVO with increasing RV-PA gradients, but in those dogs with the greatest RV-PA pressure gradients, no change in baseline RVO-MSL was noted.

These studies indicate that (1) dogs with left-to-right shunts respond to isoproterenol with decrease in the shunt, which may be secondary to altered tonus of the RV, and (2) earlier contraction of the RVO plays a part in the genesis of the RV-PA gradients seen in some left-to-right shunts.

Clinical Considerations in the Surgical Management of Strokes (P)

Jesse E. Thompson, Mark M. Kartchner, Dale J. Austin, Clarence G. Wheeler, and Ralph D. Patman, Dallas, Texas

Carotid endarterectomy has become increasingly important as definitive management of cerebrovascular insufficiency secondary to cervical carotid occlusions. During eight years we have performed 400 carotid operations on 320 consecutive private patients with significant arteriosclerotic lesions demonstrated by bilateral carotid arteriography. Operative technique consists of endarterectomy under general anesthesia using an inlying shunt.

Patients were classified into four groups: (1) frank stroke (135 patients), (2) transient cerebral ischemia (151 patients), (3) chronic cerebral ischemia (13 patients), and (4) asymptomatic carotid bruit (21 patients). Long-term follow-up is 100% complete.

Over-all operative mortality was 3.5% (14 of 400). Operative mortality in frank strokes was 7.4% (12 of 163), in transient ischemia 1.02% (two

of 196), and zero (0 of 41) in chronic ischemia and asymptomatic bruits. Morbidity was minimal.

Of 60 late deaths only six were from strokes; 29 were cardiac deaths. Among long-term frank stroke survivors, 42.8% (39 of 91) are normal, 48.4% (44 of 91) are improved, and none has had a subsequent stroke. In transient ischemia survivors, 90% (116 of 129) are normal and 7.8% (ten of 129) improved. There was no subsequent stroke on the side originally involved; however, three patients had contralateral strokes due to unoperated lesions. The remaining two groups had no strokes.

Endarterectomy is most useful for transient cerebral ischemia. It should probably not be used for rapidly progressive or catastrophic strokes. Its cautious application for chronic cerebral ischemia and asymptomatic bruits is warranted. Carotid endarterectomy is safe, definitive therapy in selected patients with stroke syndromes.

Volume of the Major Lymphatic Channels of Dogs

Sam A. Threefoot and James Pearson, New Orleans, Louisiana

Because of reported consequences of deposition of radiopaque oil in lungs following lymphography, the capacity of lymphatic channels from the foot to the cervical thoracic duct has acquired significance other than usefulness in calculations of water, electrolyte, and protein transport.

The volume of colored or radioactive iodinated poppyseed oil, albumin, or dextran injected into a pedal lymphatic was recorded, either when it appeared in a thoracic duct cannula or when radioactivity was detected in the superior vena cava. In ten of 12 animals, the average volume of iodinated poppyseed oil was 5.5 ml (3.3 to 9.0). In two, oil did not appear until five and 50 minutes after injection of 10 ml was completed. In six animals the average volume of albumin or dextran was 3.8 ml (1.5 to 6.0). The difference is attributed to greater viscosity of the oil and retention in nodes.

Although there was a rough correlation with body weight, distensibility of lymphatics (nodes and channels) seemed to be a more important determinant of volume injected before appearance at the neck. Droplets of lymph intermixed with the oil observed in the cannula, and gaps in the column of opacity on X-ray indicated that because lymph entered the main channels from tributaries during the continuous injections, recorded volumes were less than the actual volume of the system. Planimetric measurements of radiopacities also indicated incomplete filling with tracer. Recorded volumes were significant, however, since they reflected the quantity required to reach the venous system for deposition in the lungs.

Comparison of Medium and High Intakes of Sodium as a Sole Treatment for Severe Postural Hypotension

Louis Tobian and Judith Meuli, Minneapolis, Minnesota

Dietary salt was varied during four periods in a tabetic patient with severe postural hypotension. He was progressively tilted each day to find the angle of tilt which lowered his systolic pressure to 65 mm. During period I (14 days), he ate 7 g salt daily and required an average tilt of 7.0° to reach 65 mm. During period II (18 days), he ate 30 g salt daily and required an average tilt of 26.1°. During period III (19 days), he ate 7 g salt daily plus placebo pills and required 12.5°. During period IV (25 days), he ate 37.2 g salt daily and required 38.3 degrees of tilt (significantly higher than periods I, II, and III). Symptoms closely paralleled tilt data. He could walk without fainting during periods II and IV but not during periods I and III. His daily supine blood pressures averaged 98/59 in period I, 144/83 in II, 120/69 in III, and 156/86 in IV. Plasma volume was 3,422, 4,125, 3,326, and 3,700, and blood volume was 4,720, 5,156, 4,964, and 5,136 in the successive periods. Supine cardiac output averaged 5.1, 5.9, and 5.0 L in periods I, II, and III.

A high salt intake alleviated symptoms, objectively increased tolerance to tilting, and significantly elevated supine blood pressure. The effects of a high salt intake can be partially explained by an increase in blood and plasma volume and an increase in cardiac output. The high salt intake is an effective treatment for severe postural hypotension.

Primary Myocardial Disease in the Alcoholic Patient (P)

John R. Tobin, Jr., Chicago, Illinois, John F. Driscoll, Spokane, Washington, Manuel T. Lim, George C. Sutton, and Rolf M. Gunnar, Chicago, Illinois

Forty individuals with primary myocardial disease (PMD) and alcoholism were studied. Prerequisites for inclusion were age under 50, unequivocal heart disease of undefined etiology, and detailed history of alcoholism.

Clinical characteristics separated patients into two groups. In group I (22 patients), palpation of point of maximum impulse (PMI) disclosed a discrete, sustained apical heave. Atrial gallop sounds (S4) were audible in 17, and ventricular

gallop sounds (S3) were audible in 14. Roentgenograms disclosed concentric left ventricular hypertrophy with or without dilatation. When the patient was in congestive heart failure, mild diastolic hypertension was present, and when compensated, the diastolic hypertension disappeared. In group II (18 patients), palpation of PMI disclosed a diffuse, active, apical heave. S4 was audible in five, and S3 was audible in ten. Atrioventricular regurgitant murmurs were heard customarily on admission; roentgenograms disclosed gross cardiac enlargement, and congestive heart failure was resistant to therapy. The average duration of congestive heart failure was 7.5 months in group I and 20.7 months in group II ($P < 0.05$). No other significant differences were noted between groups.

Serum complement fixation titers were obtained with a panel of viral antigens in 38 patients and disclosed changes in antibody titers in 16. These antibody levels could not be correlated with epidemiological or clinical evidence of infection and may result from viral latency, anamnestic response, or an altered immune mechanism.

Exploratory mediastinotomy and myocardial biopsy were done in nine patients. These procedures tended to confirm clinical groupings. Histological studies of myocardium revealed diffuse interstitial fibrosis and myocardial hypertrophy. No active myocarditis was found.

Difficulties of Differentiating Streptococcal Infection from the Carrier State Among Children with Nasopharyngitis (P)

Franklin H. Top, Jr., and Lewis W. Wannamaker, Minneapolis, Minnesota*

The significance of group A streptococci isolated from children with uncomplicated nasopharyngitis was investigated. Patients were examined, cultured, and bled initially and three and six weeks later. Thirty-four per cent (89 of 259) of the patients harbored beta hemolytic streptococci; 86% (77 of 89) of these strains were group A streptococci, and 44% (34 of 77) were M-typeable. Patients harboring group A streptococci had symptoms and physical findings similar to those of patients not harboring these organisms, except for a higher prevalence of exudate, cervical node tenderness, and polymorphonuclear cells on pharyngeal smears. Only seven of the 49 patients (14%) who harbored group A streptococci and whose sera were examined for antidesoxyribonuclease B (anti-DNAse B) showed a two-tube rise between acute and convalescent sera. Twenty-six of 42 patients in whom no rise was demonstrated (62%) had acute phase titers of greater than 250 units. The low number of patients with an antibody response and the large number with nontypeable organisms and a high initial titer suggest that most of the patients with nasopharyngitis and with group A streptococcal isolates did not have a presenting streptococcal infection but were carriers, many as a result of a recent streptococcal infection. These data indicate the difficulties of differentiating true streptococcal infection from the streptococcal carrier state with superimposed nonstreptococcal infection. The findings emphasize the dilemma of differential diagnosis in attempting to apply primary prophylaxis to pediatric populations.

Renin Activity and Effect of Angiotensin on Blood Pressure and Differential Renal Function in Hypertensive Man (P)

Ross M. Tucker, James C. Hunt, Frank C. Maher, Sheldon G. Sheps, and Laurence F. Greene, Rochester, Minnesota

Twenty-five patients with hypertension and parenchymal renal disease, renal artery stenosis, or essential hypertension had renal arteriography and additional studies, including measurement of renin activity in peripheral venous blood, angiotensin infusion test, and differential renal function studies before and during angiotensin infusion (half the dose required to elevate diastolic blood pressure by 20 mm Hg).

Patients with primary hypertension had normal renin activity and a variable but generally low-dose pressor response to infused angiotensin, which in "half-pressor" doses resulted in diminished glomerular filtration and renal plasma flow and a saluresis and diuresis by the separate kidneys.

Patients with hypertension and parenchymal renal disease had normal renin activity, a low-dose pressor response to angiotensin, and variable changes in renal hemodynamics but no saluresis or diuresis with "half-pressor" doses of angiotensin.

Patients with renovascular hypertension had increased renin activity and required larger doses of angiotensin to obtain a pressor response. During angiotensin infusion, function of the kidney with the stenotic renal artery was diminished as follows (average percentage change from pre-angiotensin values): inulin clearance 40%, PAH clearance 60%, sodium excretion 30%, and urinary volume 50%. The contralateral kidney had minor clearance changes, but sodium excretion and urinary volume increased by 60% and 50%, respectively.

Increased renin activity in peripheral venous blood, relative resistance to the pressor effect of infused angiotensin, and diminished clearance of insulin and PAH, as well as renal excretion of sodium and water, correlated well with arterio-

graphically demonstrated, functionally significant renal artery stenosis in hypertensive man.

Femorotibial Bypass (P)

R. Robert Tyson and Dominic A. DeLaurentis, Philadelphia, Pennsylvania

The use of arterioplastic procedures, such as bypass, endarterectomy, and replacement, in the treatment of occlusive arterial disease has been well documented. The application of these procedures, however, has been limited to the larger arteries. There are few reports in the literature pertaining to the use of these procedures distal to the popliteal artery. Except for recent laboratory experience with small vessel surgery, the use of arterioplastic procedures in vessels such as the anterior and posterior tibial arteries has been very discouraging.

We wish to report the results obtained when the anterior or posterior tibial artery of the leg formed the distal end of a bypass. Autogenous saphenous vein was used in all cases. The tibial arteries ranged between 1.5 and 2.5 mm in diameter. The age range was 41 to 79. Very severe ischemia and threatened loss of the limb were the indications for the surgical procedures.

The techniques used were similar to the methods used on larger vessels. Magnification, small instruments, and attention to detail are the necessary requisites. Careful arteriography is essential to the proper selection of patients.

Eleven patients were explored; one was deemed not suitable for bypass, and in ten bypass was performed. Eight have remained open for periods of two months to 23 months, resulting in preservation of the extremity.

Acute Myocardial Infarction in 100 Consecutive Cases: Results in Intensive Coronary Care Unit Compared with Open Service Cases (P)

Paul N. Unger and Adeline C. Jenkins, Miami Beach, Florida

One hundred cases of acute myocardial infarction admitted to an intensive coronary care unit (ICCU) were compared to 144 acute infarctions admitted to open divisions (OD). Gross mortality rates for the groups were the same, with the ICCU group 28% (28 of 100) and the OD 29% (42 of 144). However, when those patients who expired within the first 24 hours, 50% (14 of 28) in ICCU and 28% (12 of 42) OD are withdrawn from both groups, the mortality rate for ICCU was 16% (14 to 86) compared with OD 23% (30 of 132). Mortality in shock was the same for both groups. Atrial tachycardias had poor prognostic significance with 41% (16 of 39) of the ICCU group ultimately expiring. Mortality among successfully treated ventricular tachycardias was 66% (16 of 24). No case of ventricular fibrillation survived (12 of 12), even with successful defibrillation, and no case of asystole with external pacing survived. Conclusions drawn indicate that results in atrioventricular (A-V) block should be improved by use of internal pacing with transvenous bipolar electrode catheters inserted in second or third degree A-V block.

Urgent need exists for further development of new techniques for management of "pump failure." Highest possible salvage rates can be achieved now if all patients with acute infarction are admitted to and kept in coronary care units initially for ten to 14 days, rather than limiting use of these special facilities only to seriously ill patients.

Cardiac Resuscitation with Hydrogen Peroxide

Harold C. Urschel, Jr., James W. Finney, Andres R. Morales, George A. Balla, and John T. Mallam, Dallas, Texas

Ventricular fibrillation or cardiac arrest resulting from myocardial ischemia or anoxia in hearts which could not be resuscitated by conventional techniques could be reversed to regular sinus rhythm by the regional application of dilute hydrogen peroxide. Hydrogen peroxide is converted to high atmospheric equivalents of oxygen, and with regional application systemic oxygen toxicity is avoided.

Ventricular fibrillation or cardiac arrest was produced in 40 rabbits by tracheal occlusion or circumflex coronary artery ligation. Regional application of 0.12 to 24% hydrogen peroxide via coronary artery infusion or epicardial application returned the heart to regular sinus rhythm and elevated blood pressure to normal, in contrast to ten control animals who could not be resuscitated with standard methods. The procedure was repeated in ten goats undergoing anterior descending coronary artery ligation. The electrocardiogram, arterial and venous pressure, pH, and myocardial tissue oxygen tension were monitored. Myocardial tissue oxygen tension values increased from two to six times control values following hydrogen peroxide application. Low molecular weight dextran and papaverine improved effective coronary artery infusion of hydrogen peroxide. Dimethyl sulfoxide may improve diffusion in the thick myocardium.

Following the failure of conventional resuscitation methods, hydrogen peroxide was employed in one human case with temporary reversal of ventricular fibrillation to regular sinus rhythm and elevation of the blood pressure to normal.

Capillary Obstruction in Experimental Cor Pulmonale

Enrique Valdivia, Yuzo Hayashi, Joseph J. Lalich, and Jayashree Sonnad, Madison, Wisconsin

Guinea pigs exposed to simulated high altitude in low pressure chambers develop pulmonary artery hypertension and right ventricular hypertrophy. Cineangiographic studies, postmortem pulmonary arteriography, and histological observations demonstrate a lack of capillary visualization and dilatation of the precapillary vessels. Monocrotaline injected subcutaneously produces pulmonary edema, hemorrhage, arteritis, and thrombosis in rats. Animals that survive the acute episode develop right ventricular hypertrophy.

This report includes three groups of guinea pigs submitted to experimental hypoxia. The first group was exposed to 12,500 feet for a year or more. The second group was exposed to 18,000 feet for six or more weeks. The third group was exposed to 18,000 feet for 48 hours. The lungs of these animals were studied with the light and electron microscopes. Pulmonary capillaries were found to be plugged by accumulations of platelets. A similar lesion was observed in rats injected with monocrotaline. Two groups of rats were studied. The first group was composed of rats sacrificed 24 hours after the injection. The second group was sacrificed four hours after a single monocrotaline injection. The persistent finding of platelet aggregates in these two experimental models of cor pulmonale indicates that these intravascular alterations may contribute to the development of cor pulmonale. Platelet accumulations may release vasoactive substances. Platelet aggregates also trap red blood cells and leukocytes. These lesions precede the development of pulmonary edema, pulmonary arteritis, and hemorrhage and may be secondary to endothelial, alveolar wall, or hematological alterations.

Paroxysmal Ventricular Tachycardia Induced in Dogs with Chronic Complete Heart Block by Hypothalamic Stimulation (P)

Robert L. Van Citters, Orville A. Smith, Jr., Seattle, Washington, and Herbert D. Ruttenberg, Los Angeles, California

Regulation of left ventricular performance was investigated in ambulatory dogs in which cardiac conduction was permanently blocked by chemical ablation of the atrioventricular node. Twelve such dogs were chronically instrumented with ultrasonic flowmeters on the aortic root, left ventricular pressure cannulae, and electrocardiographic electrodes. Resting ventricular rates ranged between 28 and 50/min; maximal recorded ventricular rate with treadmill exercise or infusion of 2 μg/kg of epinephrine or isoproterenol was 76/min. In five of these dogs, electrodes were positioned in the cerebral cortex dorsal to the hypothalamic nuclei and advanced ventrally in 1-mm increments by means of a stereotaxic instrument. Monopolar stimulation was carried out at each level for 30 seconds with 20-v trains of 50 cycle/sec square waves of 1-msec duration. Paroxysmal ventricular tachycardia occurred at rates up to 280/min when a discrete area in the H] Fields of Forel was stimulated. The response was repeatable and was elicited in all five dogs. The area of hypothalamus involved was less than 2 mm in depth. The induced tachycardia was not due to re-establishment of atrioventricular conduction. Electrocardiographic evidence implicated repetitive discharge of single ventricular foci during stimulation. Tachycardia did not occur with infusions of catecholamines. The response to stimulation was not blocked by 15 mg/kg phenoxybenzamine.

Effects of Morphine on Ventricular Function and Peripheral Resistance and Capacitance (P)

John S. Vasko, R. Peter Henney, Robert K. Brawley, H. Newland Oldham, and Andrew G. Morrow, Bethesda, Maryland

The beneficial effects of morphine in patients with acute left ventricular failure and pulmonary edema are recognized, but little is known of the mechanisms by which this drug alters cardiovascular performance. The effects of morphine on myocardial function and peripheral vascular resistance and capacitance were studied in 30 dogs. In six dogs data were obtained for the inscription of ventricular function curves (VFC), the dp/dt of left ventricular pressure, mean ventricular ejection rate, and the tension-time index (TTI). A right-heart bypass preparation was employed which permitted a variable stroke volume while heart rate and aortic pressure were constant. Following the administration of morphine (0.5 mg/kg), myocardial contractility improved, indicated by a shift of the VFC to the left, an increased rate of ventricular ejection, and decreased TTI. Total peripheral vascular resistance (TPR) and capacitance were measured in 24 dogs with a cardiopulmonary bypass system in which momentary changes in circulating blood volume could be determined. Following the administration of morphine (1 mg/kg), TPR decreased 10 to 78% (mean 32%) and 9 to 36% (mean 30%) of the estimated blood volume pooled in the capacitance vessels.

The data indicate that cardiac performance is augmented by morphine, but the predominant mechanism by which the drug benefits the patient with pulmonary edema is apparently a

"pharmacological phlebotomy," the result of increased peripheral vascular capacitance.

Coronary Angioscannography

Manuel Viamonte, Jr., James R. Jude, Carlos R. Lombardo, and Albert J. Gilson, Miami, Florida

Arteriography provides adequate evaluation of arteries and veins usually no smaller than 0.3 mm in diameter. Magnification radiography with special X-ray tubes permits resolution of vessels as small as 0.1 mm, but rapid sequential filming is then not possible. Injection of macroaggregates of radioactive serum albumin, using particulate size between 100 and 500 μ permits scanning and studies of the microcirculation (small arteries and arterioles). Both techniques (angiography and scannography) complement each other. We have studied the coronary circulation by combining the angiographic study with scanning of the heart after the infusion of macroaggregates directly into the coronary arteries.

Ischemic changes are depicted in the dog only when five times the volume of macroaggregates necessary for an adequate heart scan are injected. The vascular territory of occluded branches of the coronary arteries is demonstrable in the scan and correlates with the "negative" myocardiogram that appears in the angiographic study.

Revascularization of the Entire Heart by Internal Mammary Artery Implantation, Epicardiectomy, and Free Omental Graft Operation (P)

Arthur M. Vineberg, Montreal, Quebec, Canada

The internal mammary artery operation revascularizes mainly the left ventricle. A supplement to this basic operation is needed to treat right and left coronary artery disease.

Numerous operations have been tested against triple coronary artery ameroid constriction, which causes 100% mortality in the animal. These have been evaluated with reference to survival of animal, myocardial damage, and development of extracardiac coronary anastomoses.

The free omental graft operation with epicardiectomy and the internal mammary artery implant combined with free omental graft and epicardiectomy operation form such extensive extracardiac coronary anastomoses that 75% and 79% of the animals, respectively, survived. The majority did so without myocardial damage.

The rapidity with which the free omental graft forms multiple anastomoses with right and left ventricles has permitted treatment of patients with angina at rest without exciting cause. It has been used in combination with internal mammary artery implantation and epicardiectomy in 62 cases. 47 of which have been followed up to three years.

Many angina decubitus bed-chair cripples, formerly rejected for implantation alone, have been treated successfully with the combined operation. Cases with multiple myocardial infarctions have been accepted. The operative mortality has been 5% and the over-all improvement 88% (no angina at rest). Criteria for selection, importance of coronary cineangiography, and full details of postoperative results are included in the report.

Role of Beta Adrenergic Receptors in the Regulation of the Pulmonary Circulation

John H. K. Vogel‡ and S. Gilbert Blount, Jr., Denver, Colorado

The purpose of this study was to evaluate the effects of beta receptor blockade on the pulmonary circulation. Propranolol (P), a potent beta adrenergic receptor blocker, 0.074 to 0.092 mg/kg, was administered to five human subjects during right-heart catheterization. The effects of P on resting dynamics, hypoxia, isoproterenol, and exercise were recorded. Also, observations were obtained in five calves, aged three days to four months.

There was an increase in pulmonary arterial pressure (PAP) and total pulmonary resistance (TPR) in all subjects following P. With hypoxia, exercise, or isoproterenol, TPR was greater than before P. Heart rate and cardiac output were decreased after P with variable changes in systemic arterial pressure. A square-wave response to the Valsalva maneuver was noted after P. In two subjects mild infundibular pulmonary obstruction was abolished. Similarly in all calf studies there was a rise in PAP associated with a decrease in cardiac output and heart rate. Moreover, after beta blockade, hypoxia elicited higher PAP and TPR.

The results suggest that after P the pulmonary vascular bed functions on a different pressure-flow curve, as a result of pulmonary arterial vasoconstriction. Moreover, it is apparent that beta receptors are active in the newborn animal.

It is concluded that beta receptors play an active role in regulation of the pulmonary circulation.

Criteria for Use of Internal Cardiac Pacing

John T. Vookles and P. Milnor, Jr., Memphis, Tennessee

Criteria for the use of internal cardiac pacing (ICP), either bipolar electrode catheter or implantable pacemaker, in complete atrioventricular

block (CHB) have been restricted to the Stokes-Adams syndrome and intractable congestive heart failure. To evaluate the adequacy of these criteria, 52 consecutive cases of CHB have been studied. The cases were divided into two groups. Group A (25 patients) never fulfilled these criteria. Group B (27 patients) did fulfill these criteria, and 20 of these patients were treated with ICP. Fifty-six per cent (14 of 25 cases) in group A expired in the hospital. Nineteen per cent (five of 27 cases) in group B expired in the hospital, but only three of the five had been treated with ICP. Because of the disparity in the mortality rates for the two groups, all cases in group A were reviewed. Six cases were found in which ICP could have been expected to alter the outcome of the illness. It is concluded that the criteria for the use of ICP in the management of CHB should be expanded and that ICP should be used more often (1) in emergency resuscitative situations and (2) in some situations of asymptomatic complete heart block.

Improved Prognosis in Treated Malignant Hypertension

Ignatios J. Voudoukis, John R. Caldwell, Robert W. Anderson, and Sarjit Singh, Detroit, Michigan

Seventy-eight cases of malignant hypertension were seen from 1952 to 1962. The criteria for diagnosis were papilledema, retinal hemorrhages and/or exudates, and established diastolic hypertension. Forty-three patients were males and 35 females; 67 were whites and 11 Negroes, and their average age was 48 years. Long-range results in patients with close follow-up revealed the following: regression of papilledema, hemorrhages, and exudates in 84% (21 of 25), reduction in blood pressure in 78% (18 of 23), regression of proteinuria in 52% (12 of 23), reduction in left ventricular hypertrophy in 43% (ten of 23), and decrease in serum creatinine in 38% (eight of 21). In order to investigate whether or not modern antihypertensive therapy with sulfonamide saluretics and sympathetic inhibitors have influenced the prognosis of this disease, survival rates for the 65 cases seen from 1952 to 1959 were estimated. Fifty cases first seen prior to 1958, that is, in the pre-thiazide years, had survival rate for one year 46% (23 of 50), three years 18% (nine of 50), and five years or more 14% (seven of 50). By contrast, the survival rates for the 15 patients first seen from 1958 to 1959 were for one year 93% (14 of 15), three years 86% (13 of 15), and five years or more 80% (12 of 15). In general, there was an inverse relationship between the degree of azotemia and years of survival.

The results indicate that in the absence of severe azotemia, with effective antihypertensive therapy, particularly after the addition of thiazides and sympathetic inhibitor drugs, the prognosis for patients with malignant hypertension has greatly improved.

Explanation for Glomerular Susceptibility to Injury in Renal Disease (P)

W. Gordon Walker, Baltimore, Maryland

Most diffuse renal diseases produce much greater glomerular than tubular damage. In search of an explanation for this increased glomerular susceptibility, a means of obtaining isolated glomeruli for metabolic study has been devised. These glomeruli showed greater incorporation of labeled amino acids into protein than did corresponding preparations of tubular tissue. Rate studies revealed that C^{14}-lysine was incorporated into glomerular protein at ten times the rate in tubule cells. This incorporation was facilitated by glucose and did not occur in the absence of an energy source. The use of 10^{-5} M puromycin produced 80% inhibition of this incorporation rate. Incubations with H^3-cytidine yielded a glomerular RNA fraction which was rapidly labeled with tritium. The quantity of labeling increased linearly with time; in contrast, very little labeling could be demonstrated in tubule cell RNA. Although 10^{-5} M actinomycin produced 90% inhibition of tritium labeling in glomerular RNA, puromycin was without effect. The rapid labeling of glomerular protein with C^{14} amino acids, inhibition of C^{14} incorporation by puromycin, rapid labeling of glomerular RNA with H^3-cytidine, and inhibition of this RNA labeling with actinomycin but not puromycin—all point to much greater rate of synthesis of protein by glomeruli than by tubules. Rate studies indicated that protein synthesis per unit weight of glomeruli was eight to ten times as great as that per unit weight of tubules.

These observations suggest that the greater metabolic needs of glomeruli may render them more susceptible to injury in renal disease.

Myocardial Infarction in Young Men

Weldon J. Walker, Los Angeles, California, and Gabriel Gregoratos, Washington, District of Columbia

The medical histories and findings of 100 military personnel who survived a transmural myocardial infarction at age 40 or less were compared with those of 72 age-matched military controls, chiefly individuals hospitalized for fractures. Each group completed identical questionnaires concern-

ing their personal habits and family histories. Striking differences were found between the two groups.

Patients who had sustained a myocardial infarction had higher serum cholesterol levels, higher total serum lipids, were more overweight, had more hypertension, and gave a more frequent family history of coronary artery disease to a highly significant degree ($P < 0.001$). The coronary patients were shorter in stature, considered themselves under more emotional tension, used less unsaturated fats in their diets, and had sustained a greater weight gain during military service in comparison with the controls; these differences were also very significant ($P < 0.01$). Significant differences ($P < 0.05$) also existed between the two groups in that the coronary patients smoked more cigarettes and gave a history of eating more saturated fats. On the other hand, no significant difference was found in coffee consumption, alcohol consumption, chest expansion, hematocrit, family history of diabetes mellitus, history of peptic ulcer, or frequency and extent of baldness.

The study of individuals who manifest atherosclerosis in early life should more clearly define etiological and predisposing factors of the disease and afford fruitful clues for its prevention.

Extrasystoles and Ectopic Tachycardias due to Re-entry Within a Focal Zone of the Intact Ventricle (P)

Andrew G. Wallace and Robert J. Mignone, Durham, North Carolina

Recent experiments have suggested that nonuniform properties of conduction or recovery in adjacent regions may create the conditions for re-entry. These studies were designed to examine whether or not a focal electrophysiological alteration within the intact ventricle can lead to extrasystoles as a result of re-entry.

Studies were performed on dogs with the heart exposed. Pacing wires were attached to the right atrium and connected to a network designed to drive the heart at a basic frequency (A_1A_1) and to introduce a premature beat (A_2) every sixth cycle. A 2- by 2-cm silver coil was implanted on the right or left ventricle, and ice water was circulated through the coil to produce a regional zone of hypothermia. Electrical activity was recorded by means of a multipolar electrode advanced through the coil to the endocardium.

For A_1 and A_2, normal activation spread rapidly from endocardium to epicardium. When the myocardium under the coil was cooled, conduction of A_1 was slowed, and at short A_1A_2 intervals A_2 was markedly delayed or blocked on transit to the epicardium. At appropriate A_1A_2 intervals A_2 was sufficiently delayed in the subepicardial region to re-enter the endocardium and initiate a coupled ventricular extrasystole. On occasion A_2 was followed by repetitive extrasystoles originating from under the coil. Nonstimulated responses could be abolished by rewarming.

These observations suggest that electrical nonhomogeneity within the ventricle can lead to extrasystoles as a result of re-entry. Multiple responses initiated from the hypothermic region suggest that focal circus movement or repetitive re-entry can lead to ectopic tachycardia.

Management of Malfunctioning Implanted Cardiac Pacemakers

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Seventy-four patients have had implantations of pacemakers from October, 1962, to May, 1965. In 30 of these (40%), there were 55 pacemaker failures. An approach was designed to diagnose and manage these life-threatening emergencies: (1) immediate hospitalization; (2) immediate control of heart rate if indicated; bipolar catheter is inserted if the patient is syncopal or if a thoracotomy proves necessary; (3) electrocardiogram with the patient in various positions; (4) roentgenography with cinefluorography; and (5) definitive testing and repair (local anesthesia) of the generator or extrathoracic electrode splicing. An anesthesiologist should be in attendance for an emergency or a thoracotomy. Myocardial threshold requirements are tested by unipolar stimulation with a variable output generator. The pacemaker generator is tested with an oscilloscope and 1,000-ohm resistance. If both leads are broken within the chest, thoracotomy and replacement are carried out. If one electrode is broken, the unit is unipolarized. If the generator is faulty, a generator replacement is performed. If the myocardial threshold is elevated, the generator output is increased.

Evaluation of 55 malfunctions showed seven generator failures. There were 28 instances of electrode breaks with 12 fractures in the myocardium. Twelve required an increased energy output to stimulate the heart, four being associated with polarization from a d-c leak. All eight not associated with d-c leak occurred at three months after implantation. This is probably associated with a high initial threshold at the time of the expected sudden increase in output which occurs in mercury batteries after three months of use. There has been no hospital mortality in the management of these pacemaker complications.

Cardiac Output Response to Hyperbaric Oxygenation at Rest and During Exercise

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The response of cardiac output (CO) to hyperbaric oxygenation (OHP) in normal adult males was studied at rest and during exercise on a bicycle ergometer with a fixed work load of 600 kpm/min. The CO was measured by the Stewart-Hamilton formula, using indocyanine-green dye. O_2 was delivered through a low dead-space mouthpiece with a demand valve. Arterial oxygen tensions (pO_2) were measured with a Clark macroelectrode and the Astrup equipment.

At rest the CO and pO_2 under given conditions were as follows: (1) 1 atm, breathing room air, 6.08 L/min and 116 mm Hg, respectively; (2) 1 atm, breathing 100% O_2, 6.09 L/min and 584 mm Hg; (3) 2 atm, breathing 10.5% O_2, 6.02 L/min and 116 mm Hg; (4) 2 atm, breathing 100% O_2, 5.96 L/min and 1,204 mm Hg; (5) 3 atm, breathing 7% O_2, 6.25 L/min and 137 mm Hg; and (6) 3 atm, breathing 100% O_2, 5.86 L/min and 1,993 mm Hg.

During exercise the CO and pO_2 under given conditions were as follows: (1) 1 atm, breathing room air, 17.69 L/min and 113 mm Hg; (2) 1 atm, breathing 100% O_2, 15.42 L/min and 560 mm Hg; and (3) 2 atm, breathing 100% O_2, 13.92 L/min and 1.210 mm Hg.

Under the above conditions, OHP was associated with a significant decrease in CO during exercise in every subject. No significant effect of OHP on CO was found at rest or as a result of increased pressure without increased oxygenation.

Disseminated Pulmonary Arterial Thrombosis Associated with Thrombocytopenia: Occurrence in Identical Twins (P)

Yang Wang, Arthur H. L. From, William Krivit, Martin A. Segal, Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

In both members of a set of identical female twins, pulmonary hypertension developed when the subjects were 17 years old. The basis for the pulmonary hypertension, as later proven by necropsy, was disseminated thrombosis within the pulmonary arteries, although thrombotic lesions were not found in the other organs at necropsy. No evidence of a systemic disease was uncovered in either patient. The only significant hematological abnormality was thrombocytopenia in both. In the one patient in whom anticoagulant therapy was instituted, there was a rise of platelets to near-normal levels, suggesting that the thrombocytopenia was due to sequestration of platelets in thrombi.

Quite apart from the occurrence in twins, the cases suggest an entity, as yet undefined, in which pulmonary arterial thrombosis is the principal overt expression.

On-Line Classification of Vectorcardiograms for Diagnosis of Congenital Heart Disease (P)

Homer R. Warner, T. Allan Pryor, and Albert S. Johnson, Salt Lake City, Utah

Experience in this laboratory with computer diagnosis of congenital heart disease has shown that differences in physician interpretation of input data represent the largest source of error. A digital computer program has been written for estimating the probability that any given vectorcardiogram (VCG) represents each of five patterns, namely, normal, right ventricular hypertrophy, left ventricular hypertrophy, right bundle-branch block, and left bundle-branch block. Three orthogonal VCG leads are fed directly to a computer interface where an eight-bit sample of each lead is obtained each millisecond. Each QRS complex is isolated by the program, and the amplitude of each point is quantitized into one of ten levels. A coincidence matrix is generated by adding a number at each point in time to the matrix element which represents the levels for leads x, y, and z. The number added at each point is weighted to represent the position the measurement occupies within its level. Such matrices are generated from a series of representative VCG for each of the five classifications and stored on a library magnetic tape. The unknown VCG to be classified is then converted to a matrix in a similar fashion, and a point-by-point correlation between this matrix and each of the "known" patterns is performed. These correlations serve as a basis for classifying the unknown VCG into an appropriate form for input into a congenital heart disease diagnosis program.

Anthropometric and Sociological Factors Related to Blood Pressure Among Female Negro High School Students in Hinds County, Mississippi (P)

Robert L. Watson and Herbert G. Langford, Jackson, Mississippi

Negro girls in grades 9 through 12 in Hinds County, Mississippi, were examined to obtain baseline blood pressure data for a prospective study.

A total of 2,589 subjects are included in the study. Blood pressure and pulse rate were measured by a Negro nurse, and measurements were

taken after five or more minutes of rest in the sitting position. Independent measurements of pressure were obtained both by a standard sphygmomanometer and a sphygmomanometer developed at the London School of Hygiene and Tropical Medicine. Height, weight, arm circumference, and triceps skinfold were also measured. One of the rural schools had been surveyed two years previously by a Caucasian physician, and the recorded pressures were available for comparison.

There was close agreement between the mean pressures obtained using both apparatus (within 2 mm Hg), but there was a marked digit preference with the standard sphygmomanometer. Diastolic measurements were less reproducible than systolic measurements.

The crude systolic mean for urban subjects was 108.8 mm Hg and for rural subjects 115.3 mm Hg. In the urban school, which appeared to serve the highest economic group, the systolic mean was 103.9 mm Hg. The systolic mean for the rural school obtained previously by the white observer was 122.1 mm Hg, as compared with 116.4 in our study.

There appear to be at least two factors affecting our recorded blood pressures, one related to race and rank of the observer and one related to urban-rural economic differences.

Metabolic Inhibitors of Perfused Rat Hearts (P)

Watts R. Webb, Ross P. Dodds, Jr., Armand M. Karow, Jr., and William A. Cook, Dallas, Texas

Hearts of heparinized albino rats were isolated and perfused on a Langendorff perfusion column, using a modified Ringer's solution (37.5) containing glucose but no insulin. After a control period of five minutes, the hearts were perfused with aliquots of sodium fluoride and adrenochrome until all contractions ceased. Hearts were then removed from the column and allowed to rest in an electrolyte bath at room temperature for periods ranging from 30 minutes to four hours, after which time they were returned to the column and perfused with a recovery perfusate composed of plain perfusate plus aliquots of glutathione, magnesium sulfate, norepinephrine, and insulin, which reversed the action of the metabolic inhibitors. Control hearts would usually function after standing for two minutes, rarely after three minutes, and never after five minutes. The metabolically arrested hearts would always function after 30 minutes (70 experiments) of nonperfusion, and five of 16 hearts functioned after an hour and two hearts even at four hours, with a grossly normal heart beat, electrocardiogram, and the development of normal tension (myographs). The hearts continued to function normally during the subsequent hour of observation.

These pilot experiments substantiate the theory that chemical inhibitors can prolong ischemic time, previously achieved only with deep hypothermia, and point the way to further investigations that may be of utmost importance in cardiac surgery and transplantation.

Effects of Hyperbaric Oxygenation on Excess Lactate Production in Exercising Dogs

William B. Weglicki, Robert E. Whalen, and Henry D. McIntosh, Durham, North Carolina

Excess lactate (XL) has been considered a reliable indicator of tissue hypoxia during exercise. This study was designed to determine whether hyperbaric oxygenation (OHP) could decrease XL formation in anesthetized dogs subjected to a standardized form of exercise. Group I (eight dogs) was exercised initially at 1 atm while breathing air and then at 3 atm while breathing 100% O_2; group II (eight dogs) was exercised at 3 atm while breathing O_2 and then at 1 atm while breathing air; group III (eight dogs) was exercised twice at 1 atm while breathing air. The two exercise periods for each group were 45 minutes apart. Resting arterial pO_2 values in groups I and II during OHP were comparable (1,893 and 1,863 mm Hg). In group I arterial XL during exercise decreased from 1.52 mM/L at 1 atm to 0.22 mM/L at 3 atm ($P < 0.01$); venous XL values decreased from 1.37 to 0.04 mM/L ($P < 0.005$). All dogs in group I demonstrated XL production at 1 atm, whereas four dogs had no XL production at 3 atm. Group II arterial XL production during exercise at 3 and 1 atm was essentially the same (0.44 and 0.32 mM/L); venous XL was comparable (0.38 and 0.49 mM/L). There was no significant difference in XL in group III animals during two exercise periods. These data indicate that OHP can diminish XL levels in exercising dogs. They further suggest that the effects of exposure to OHP persist for at least 45 minutes, resulting in diminished XL levels during subsequent exercise.

Failure of Pentaerythritol Tetranitrate to Influence Relative Coronary Blood Flow as Measured by Precordial Scanning

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The effect of pentaerythritol tetranitrate (PETN) on relative coronary blood flow was studied by precordial scanning. This technique employs mathematical analysis of the precordial radiocardiogram and peripheral arrival time following in-

travenous injection of radioiodinated serum albumin. Expressed in blood volumes per minute, the average flow for coronary patients is 0.06 and for normal individuals 0.09. Each test consists of four serial determinations to obtain an average value.

The present study included 119 subjects. Fifty-one had coronary disease, 61 were normal, and seven could not be classified with certainty. A double-blind technique was used. Pulse, blood pressure, and electrocardiograms were recorded. PETN, 80 mg, was given every 12 hours for one week following baseline studies. The study population included 60 placebo and 59 PETN-treated patients. Among 61 clinically normal subjects 55 had normal and six abnormally low relative coronary flow values. Of 51 patients with coronary disease, 31 had low values, and 20 were normal. These data indicate that the technique distinguishes normal from coronary subjects in a high percentage of instances. Among the 119 patients exposed to PETN or placebo for one week, 47 showed a change in relative coronary blood flow of more than one standard deviation. Of these, 19 showed a change in category from normal to abnormal or from abnormal to normal. Where a change of more than one standard deviation or a change in category occurred, no distinguishing pattern of response to PETN or placebo was demonstrated. The inference from the study is that PETN in doses of 80 mg twice daily for one week does not influence coronary blood flow as measured by precordial scanning, nor can the effect of this medication be distinguished from that of a placebo.

Late Circulatory Adjustments to Acute Normovolemic Polycythemia

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Previous studies of acutely induced normovolemic polycythemia (ANP) in the dog have uniformly demonstrated reduction in cardiac output (CO) and increased vascular resistances. The present study was undertaken to uncover any late adjustments to this abnormal state.

ANP was induced in 12 previously splenectomized dogs by transfusion of donor packed cells with simultaneous removal of circulating blood. Plasma volume (PV) was determined before and one-half hour after transfusion (I^{131}-albumin) and up to eight days thereafter. Red cell volume (RCV) and total blood volume (BV) were calculated from the body hematocrit and PV. In five dogs hemodynamic studies were also performed before and one-half hour after ANP and on the first post-transfusion day. Control arterial hematocrit averaged 42% (31 to 50%) and was raised to 66% (61 to 74%). PV was decreased from a control of 49 ml/kg to 30 ml/kg, while RCV was increased from 29 to 44 ml/kg. Initial CO (indocyanine-green) averaged 75 ml/kg and fell to 46 ml/kg after ANP. Stroke volume (SV) fell from 7.7 to 4.8 ml/kg. During the first 24 hours following ANP, PV rose 75% to 52 ml/kg ($P < 0.001$), and PV expansion persisted with elevated RCV throughout the study period. CO rose to 85 ml/kg ($P < 0.05$), heart rate decreased ($P < 0.05$), stroke volume increased to 10.6 ml/kg ($P < 0.01$), and left ventricular end-diastolic pressure increased ($P < 0.01$). At this time, although hematocrits were still significantly higher than prepolycythemic controls, CO had risen to prepolycythemic levels.

Rapid PV expansion appears to reverse the adverse hemodynamic effects of ANP in the dog.

Comparison of Effects of Low Molecular Weight Dextran on Blood Viscosity and the Sludging Phenomenon in Vitro and in Vivo

Roe E. Wells, Boston, Massachusetts

Since the first clinical use of low molecular weight (40,000) dextran (LMWD), the question has remained as to whether its flow-improving properties are due to a disaggregating effect on sludged blood or simply to the hemodilution produced by oncotic mechanisms. While the literature describing the salutary clinical effects of LMWD is predicated on the former mechanism, it has not yet been demonstrated in vivo or in vitro. Measurements of blood viscosity (Couette viscometer), hematocrit, total protein, fibrinogen, and sedimentation rates were made before and after the addition of 10% LMWD in saline to blood in a 1:5 dilution. Similar studies of dextran effects were made before and after the addition of fibrinogen (final concentration 750 mg% to insure erythrocyte aggregation). Control studies were made with saline, albumin, and plasma. Photomicrographs were made of the sedimentation process to record changes in cell aggregation. In vivo studies consisted of the same measurements before and after the intravenous infusion of 500 ml 10% LMWD in saline over 30 minutes with serial observations continuing for 36 hours. Blood dextran levels and photomicrographs of the bulbar conjunctival vessels for sludging were also recorded.

LMWD significantly reduced blood viscosity in vitro but less than saline or albumin did. LMWD did not significantly protect against or reverse erythrocyte aggregation effects of fibrinogen in vitro. Viscosity-lowering effect of LMWD in vivo was profound; that of equivalent infusions of saline was negligible. Conjunctival microvascular

blood flow was increased in patients with sludging during the dextran infusion.

Cardiovascular Features of Marfan's Syndrome: Family Studies

Vernon E. Wendt, Madeline K. Keech, Raymond C. Read, Americo R. Bistue, and Fernando A. Bianchi, Detroit, Michigan

Cardiovascular manifestations of the florid Marfan's syndrome are aortic dilatation, dissection, rupture, or refractory congestive heart failure. Recently, the *formes frustes* of Marfan's syndrome have been emphasized. Read et al. studied eight patients with aortic or mitral insufficiency and congestive heart failure with minimal or absent ocular and musculoskeletal involvement or aortic aneurysms. Diagnosis was made surgically by "floppy valves" and histologically by typical myxomatous degeneration and Erdheim's medial cystic necrosis. Reoperation was necessary in two for prosthetic dehiscence. The purpose of this study was to investigate the cardiovascular features of families of the six surgical survivors and four other families with Marfan's syndrome. Seventeen isolated Marfan patients were also evaluated. The 76 patients ranged in age from one to 73; 40 were female, and 36 were male. Results indicate that in families of the propositi, with rare exception, both musculoskeletal and cardiac manifestations "breed true." The electrocardiogram appeared to give the earliest evidence of the existence of cardiovascular involvement. Several patients had clinical signs of cardiac abnormality but were clinically asymptomatic. The diagnosis of rheumatic fever was made frequently in the young patient with valvular insufficiency, whereas in the older patients cardiomyopathy or arteriosclerotic heart disease was suspected. The study indicates that careful cardiovascular evaluation of the families of patients with either the florid Marfan's syndrome or *forme fruste* is important because, although widespread medionecrosis of the systemic vessels cannot be prevented, modern cardiac surgery with prosthetic valves or aortic replacement could conceivably prevent further aortic dilatation, dissection, and early death.

Hemodynamic Comparison of Isoproterenol and the Artificial Pacemaker in Patients with Complete Heart Block

Adrian S. Weyn, Makoto Takagi, Kenneth Corrin, and Samuel Bellet, Philadelphia, Pennsylvania

Certain hemodynamic events resulting from artificial cardiac pacing and isoproterenol administration were compared in patients with complete atrioventricular block. Nine investigations were made in seven subjects. The cardiac output was determined by the dye-dilution technique. A transvenous electrode catheter was used to pace the hearts at rates ranging from 60 to 130 beats/min. Isoproterenol was administered by the intravenous as well as the sublingual route. These studies were carried out at rest in all patients and during exercise in two patients. Intravenous isoproterenol consistently increased the cardiac output from 0.5 L/min to over 2 L/min (an average increase of 49%) above that obtained with the pacemaker at comparable rates. In every instance isoproterenol produced an increase in stroke volume over that produced by the idioventricular mechanism or by artificial pacing. Isoproterenol always resulted in a marked reduction of the peripheral resistance. Both intravenous and sublingual isoproterenol administered during pacing at a fixed rate produced consistent further increases in the cardiac output and stroke volume, both at rest and during exercise. The sublingual administration of isoproterenol produced similar hemodynamic responses which were of less magnitude than that induced by the intravenous route. The study reveals a much greater hemodynamic response to isoproterenol than to the artificial pacemaker. This would suggest that in patients with implanted pacemakers, the additional use of isoproterenol will further increase the cardiac output above that obtained by the pacemaker alone and thereby augment the patient's functional capacity.

Hemodynamic Responses to "Life Without Blood" (P)

Robert E. Whalen, Gordon F. Moor, F. Maxton Mauney, Ivan W. Brown, Jr., and Henry D. McIntosh, Durham, North Carolina

In 1960 Boerema demonstrated that hyperbaric oxygenation could sustain life despite the elimination of hemoglobin from an animal. To determine the hemodynamic responses of dogs completely depleted of blood, five dogs were exchange transfused with 6% dextran at 3.5 atm absolute pressure until the mean hematocrit was less than 0.3%. Arterial pO_2 before and after this procedure was essentially the same (2,166 vs. 1,021 mm Hg), but arterial O_2 content fell from 24.9 to 6.6 vol% because of the elimination of hemoglobin as an oxygen carrier. Measurements before and after substitution of dextran for blood indicated that cardiac output rose (from 1.43 to (3.11 L/min), arteriovenous O_2 difference narrowed (from 6.5 to 3.0 vol%), heart rate fell (from 158 to 122 beats/min), calculated stroke volume increased (from 9.1 to 26.2 ml), mean arterial pressure fell (from 131 to 91 mm Hg), and calculated peripheral resistance decreased

markedly (from 91.9 to 29.4 units). In vitro studies of the viscosity of blood and dextran with a cone plate viscometer indicated that at slow flow rates dextran has a significantly lower viscosity than whole blood. This lower viscosity may account for the marked decrease in peripheral resistance and increase in cardiac output noted following the substitution of dextran for whole blood in dogs. The opportunity provided by hyperbaric oxygenation to alter blood viscosity significantly by elimination of red blood cells may have certain therapeutic applications.

Control of Renin Secretion in the Dog (P)

Fred N. White, Los Angeles, California

Graded reduction in renal arterial pressure, produced by controlled constriction of the aorta, was associated with elevated renal secretion of renin-like material when mean perfusion pressure fell below 80 to 90 mm Hg. The activity was assayed in the ganglion-blocked nephrectomized rat after incubation in the presence of ethylene diamine tetra-acetic acid, an inhibitor of angiotensinase, and expressed as equivalent to angiotensin. Secretion rate was calculated as the product of renal plasma flow and the concentration of angiotensin-like activity in the renal vein plasma. Renal blood flow was determined by the use of a noncannulating electromagnetic flowmeter. Secretion rates prior to aortic constriction were of the order of 0.1 to 0.5 μg/min and 1.5 to 2.5 μg/min during aortic constriction. Significant amounts of pressor material were not found in the venous effluent of other vascular beds. Concomitant with a rise in secretion rate, there was a sharp fall in renal blood flow, glomerular filtration rate, and sodium reabsorption. After establishing an elevated secretion rate of pressor material, the secretion rate was significantly depressed by administration of mercaptomerin (2.5 mg Hg/kg), an effect which was reversed by the administration of dimercaprol (2.5 mg/kg). Infusion of 1 M NaCl or 1 M sucrose in the renal artery at a rate of 3 ml/min was also effective in suppression of the secretion of elevated levels of renin-like activity. These experiments suggest that factors other than hemodynamic alterations are primary determinants in the control of renin secretion and that tubular handling of sodium is closely linked with secretion rate.

Nonobstructive Nature of Isoproterenol-Induced Left Ventricular Pressure Gradients in Dogs (P)

Robert I. White, Jr., Kenneth B. Lewis, and J. Michael Criley, Baltimore, Maryland

Reversible obstruction of the left ventricular (LV) outflow tract has been postulated to account for the pressure gradient which can be induced in normal dogs following isoproterenol administration. An alternative mechanism for the isoproterenol-induced pressure gradients is suggested by the data from experiments conducted on 13 dogs.

LV pressure was measured through transseptal and retrograde catheters positioned in the outflow tract and apex, respectively, while aortic pressure was continuously monitored with a third catheter. Isoproterenol was administered as a constant infusion (4 to 8 μg/min) or given in bolus injections (3 to 4 μg/kg). Pressure gradients within the LV of 30 to 146 mm (average 77) were produced in seven dogs.

Left ventricular cineangiograms were taken while pressure gradients were present and during the control state. Outflow tract narrowing was not seen in any of the cineangiograms. Systolic obliteration of the apical region of the LV cavity was present in all dogs after isoproterenol. The tip of the catheter which was recording the high LV pressure was excluded from the LV cavity during systole but was clearly within the cavity during diastole. Catheter withdrawals with synchronized cinefluorographic and pressure recordings revealed that the elevated LV pressure abruptly fell to arterial systolic level as the catheter was withdrawn from the apex into the central LV cavity.

It is concluded that the LV pressure gradient induced by isoproterenol in the intact dog results from sustained (isometric) contraction about the catheter in the apex of the LV and not from outflow tract obstruction.

Effect of Left and Right Ventricular Conduction Defects on the Electrocardiogram in Muscular Subaortic Stenosis (P)

E. Douglas Wigle and Robert H. Baron, Toronto, Ontario, Canada

The electrocardiogram in 11 of 51 cases of muscular subaortic stenosis (MSS) revealed the presence of pathological Q waves in the limb leads (except aVR) and left precordial leads. Prominent R waves in the right precordial leads were present in five of these cases. Angiographic, surgical, and postmortem observations suggested that these abnormal deflections could be reasonably attributed to left-to-right depolarization of a hypertrophied ventricular septum, the vector force being directed to the right, anteriorly and superiorly. A left ventricular conduction defect (LVCD) by reducing or delaying activation of the left septal surface, should diminish these deflections, whereas a right ventricular conduction defect, by reducing right-to-left septal activation, should accentuate these deflections. Five cases with the described electrocardiographic abnormal-

ities were operated on for relief of the MSS by a vertical incision in the anterior end of the left side of the septum. This incision resulted in (1) severance of the anterior division of the left bundle branch, producing left axis deviation (left ventricular parietal block), (2) disappearance of the pathological Q waves, and (3) decrease in the right precordial R waves. Spontaneous development of complete right bundle-branch block in one case resulted in accentuation of the pathological Q waves. The observations are compatible with the concept that the described electrocardiographic abnormalities are due to left-to-right activation of a hypertrophied ventricular septum. The fact that the MSS was relieved in one case without production of a LVCD and was unrelieved in two cases in which a LVCD was produced is believed to provide strong evidence that surgical relief of the stenosis is related to the muscle-splitting incision and not to the production of the LVCD.

Dissociation of the Inotropic and Arrhythmia-Producing Effects of a Digitalis Glycoside by Potassium (P)

John F. Williams, Jr., Francis J. Klocke, and Eugene Braunwald, Bethesda, Maryland

While the ability of potassium to suppress digitalis-induced arrhythmias is well recognized, the effect of K on the positive inotropic action exerted by the glycosides on the intact heart has not been determined. Accordingly, ten anesthetized dogs were given ouabain (30 μg/kg, followed by 30 μg/kg/hr) while right ventricular contractile force was measured with a Walton-Brodie strain gauge arch. Arterial pressure and body temperature were held constant. When ventricular tachycardia or bigeminal rhythm occurred, KCl (2 mEq/kg/hr) was infused while ouabain was continued until toxicity recurred. Serum K increased from a control average of 3.2 ± 0.1 (SEM) mEq/L to 4.1 ± 0.2 mEq/L at initial toxicity and was 5.8 ± 0.4 mEq/L when toxicity recurred. Contractile force increased by an average of 64% $\pm$ 11% of control before initial toxicity developed. Myocardial force did not plateau during this period but increased progressively. Following restoration of sinus rhythm, there was a further increase in force, averaging $19\% \pm 5.3\%$ of control, before toxicity recurred. These results were not modified by adrenalectomy or by maintaining heart rate constant with right atrial stimulation. KCl infusion without ouabain did not affect contractile force. It is concluded that suppression of ouabain toxicity by KCl does not interfere with the positive inotropic effect of the glycoside but actually permits the administration of additional amounts of ouabain which produce a further increase in contractile force.

Functional Organization of Myocardial Nutritional Circulation: Effect of Nitrites (P)

Martin M. Winbury, Donald Kissil, and Manuel Losada, Morris Plains, New Jersey

The nutritional circulation of the heart was investigated by determination of the influence of coronary flow rate and "nitrites" on Rb^{86} uptake. The left coronary artery was perfused with arterial blood at several constant flow rates in anesthetized dogs and Rb^{86} extraction determined by a double-isotope procedure employing Rb^{86} and I^{131}-albumin. Clearance of Rb^{86} (C), an index of minimal nutritional blood flow, and the permeability-surface area factor (PS), an index of functional capillary surface area, were computed. C-Rb^{86} increased with total coronary inflow in a curvilinear fashion, becoming asymptotic at high flows. PS increased in hyperbolic fashion with a plateau of 80 at a coronary flow of 100 ml/min/100 g. At normal coronary flow (80 ml/min/100 g), PS was more than 85% of maximum, suggesting that the majority of capillaries were open. The effect of nitrites on C and PS depended on the control values. When C and PS were below the critical values of 50 and 80, respectively, nitroglycerin and pentaerythritol tetranitrate increased both parameters. Above these values nitrites produced a decrease or no change, even though arteriolar dilatation was always present. It is concluded that (1) at rest approximately 85% of the functional myocardial capillaries are open, (2) the remainder can be opened by nitrites, (3) "physiological shunts" are present and can divert blood from the nutritional circulation when capillary dilatation is maximal, and (4) part of the nitrite action may be due to improvement of the nutritional circulation.

Aortic Lesions and Blood Lipids in Rhesus Monkeys Fed "Table-Prepared" Human Diets (P)

Robert W. Wissler, Randolph H. Hughes, Laurence E. Frazier, Godfrey S. Getz, and Dorothea F. Turner, Chicago, Illinois

This experiment was designed primarily to furnish donor lipoproteins, which were used to induce "model" intramural aortic lesions in the other "normal" monkeys. The observations on the donor monkeys are summarized here.

Two groups of three monkeys two to three years of age each were fed an "average American diet" and a "prudent" (AHA-recommended) American diet, respectively, for 107 weeks. Daily food in-

takes were carefully measured, and after 45 weeks of feeding, serum lipid values (cholesterol, phospholipids, total lipids, and beta-lipoproteins) were consistently more elevated in those monkeys eating the "average" diet. They reached a peak at 60 weeks and then declined somewhat but still remained higher than the serum lipids of the monkeys consuming the "prudent" diet. At 60 weeks the average blood cholesterol of the three former animals was 483 mg%, while that of the latter was 318 mg%, whereas at 105 weeks they were 358 and 250, respectively.

At autopsy there was a striking difference in the degree of aortic atherosclerosis between the "average" diet-fed monkeys and the "prudent" diet-fed animals. In general, and with the exception of one very obese monkey fed the "average" diet, the animals fed the "average" American diet showed about 75% of their intimal surface involved with pale smooth plaques and fatty streaks, while the "prudent" diet-fed animals showed only 10 to 15% of their intimal surface involved.

Atrial Septal Defects in Patients over Forty-five: Merits of Surgical Versus Medical Therapy

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The role of surgery in the management of older persons with atrial septal defect (ASD) is uncertain. To determine the advantages of surgical versus medical therapy, persons with ASD 45 years and older were reviewed. There were 34 patients, 15 treated surgically and 19 medically. The history, physical findings, electrocardiographic and cardiac catheterization data, and long-term follow-up were reviewed. The average age in the nonsurgical group was 62 years and in the surgical group 52. Total follow-up period was 4.7 years in each group (range: one to 11 years in the nonsurgical group, zero to ten years in the surgical group).

The results indicated that the two groups were similar in most respects, although the nonsurgical group had slightly higher pulmonary artery pressures and pulmonary vascular resistances.

Six of 15 patients expired following surgery, three within one month and the others at six months and one and seven years. Three survivors became increasingly symptomatic postoperatively. Six were improved following surgery; however, five of these subjects were only mildly symptomatic preoperatively.

In contrast, ten of the 19 medically treated patients have minimal symptoms. Five expired, and four were lost to follow-up.

Thus, many of the group treated medically had minimal symptoms despite an average age of 62 and slightly more pulmonary hypertension. Moreover, with one exception, surgical correction was beneficial only in those with minimal symptoms and not in those who were severely symptomatic. It is concluded that surgical closure of ASD in persons over 45 is of questionable value.

Urinary Assays for Catecholamine Metabolites in Essential Hypertension and Pheochromocytoma

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Urinary specimens from 53 primary benign hypertensive, 29 pheochromocytoma, and 50 normotensive patients have been analyzed for (1) 3-methoxy-4-hydroxyphenylglycol (G) and combined normetanephrine (NM) and metanephrine (M) by a new paper chromatoelectrophoretic assay, (2) combined NM and M by a spectrophotometric assay, and (3) 3-methoxy-4-hydroxymandelic acid (VMA) by two-dimensional paper chromatography. Although the chromatoelectrophoretic assay was simpler, when either this assay or the spectrophotometric assay with readings taken at 360 μ was used, all of the pheochromocytoma patients excreted greater amounts of G and combined NM and M than the normotensive or hypertensive subjects. The means and standard deviations for G and combined NM and M in the pheochromocytoma patients with the chromatoelectrophoretic assay were 13.31 ± 18.70 and 18.32 ± 25.16 μg/1.0 mg creatinine, respectively. The latter results were not statistically different ($P < 0.05$) from those obtained with the spectrophotometric assay (360 μ), and the correlation of the individual values was good ($r = 0.55$, $P < 0.01$). Overlapping values were obtained in 11% (14 of 132) of the VMA determinations between pheochromocytoma patients and normotensive and hypertensive subjects. There was no significant difference ($P > 0.05$) in the excretion of either combined NM and M or VMA between the normotensive and the hypertensive subjects, although the means were somewhat higher and standard deviations greater in the hypertensive group. An increase in the ratio NM + M/VMA in essential hypertension could not be confirmed. It is concluded that the urinary assay for combined NM and M is more reliable than the assay for VMA in the diagnosis of pheochromocytoma.

Etiology of Mitral Regurgitation: Marfan's Syndrome

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The occurrence of varying cardiovascular abnormalities in patients with Marfan's syndrome,

particularly aortic dilatation, dissection, and regurgitation, is well recognized. However, mitral valve deformities as part of Marfan's syndrome have been recognized but reported infrequently.

Four patients (two adults, one child, and one infant) with Marfan's syndrome had significant or severe mitral regurgitation due to intrinsic deformities of the mitral valve complex and dilated sinus of Valsalva with large aortic cusps (without aortic regurgitation). Diagnosis was based on clinical, catheterization, and angiographic findings in all, with surgical correlation in two and autopsy confirmation in one.

Both adults had progressive cardiomegaly and congestive heart failure; at surgery large redundant mitral valves with associated chordal rupture were treated with plication rather than prosthetic replacement. There was improvement in both patients. Recurrence of the mitral regurgitation in one patient occurred gradually over a three-year interval, necessitating an additional surgical procedure. At autopsy the infant was found to have the basic connective tissue defect in the deformed mitral valve.

Thus, individuals with Marfan's syndrome may present with isolated, severe mitral regurgitation and subtle coexisting aortic root deformities. The mitral regurgitation may be due to the basic connective tissue defect; the abnormal mitral valve presents a site for bacterial endocarditis. Surgical approaches to valvular defects in the patient with Marfan's syndrome must be based on the appreciation of the basic connective tissue defect.

Hemodynamic Effects of Ventricular Activation Order in Experimental Purkinje Net Block

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Variations of ventricular activation sequence produced by stimulation of ventricular sites have been demonstrated to result in small hemodynamic differences when the conduction system is intact. In this study hemodynamic effects in open-chest dogs with intact conduction system (six dogs) were compared with those after surgical right bundle-branch block (RBBB) (three dogs) and after destruction of the right ventricular Purkinje net by instillation of dilute Lugol's solution (seven dogs). Stimulating electrodes on ventricular sites included the apex, both lateral walls, left base, and conus. Ventricular pressure curves were recorded with premature beats and regular drive from the ventricular sites.

With RBBB, hemodynamic variations associated with stimulation of different ventricular sites were small (up to 13% for left and 25% for right ventricular pressure in individual experiments) and were similar to those with intact conduction system.

Purkinje net destruction resulted in greater QRS prolongation than RBBB and more marked variations of peak ventricular pressure (up to 41% for the left and 31% for the right) on repetitive stimulation at different sites. Differences were greater with single premature ventricular beats or the onset of ventricular drive and decreased during regular ventricular drive. Lower right and left ventricular pressures occurred more often with stimulation of the pulmonary conus than with stimulation of other sites. With the onset of ventricular drive right ventricular pressure fell before the left, suggesting that left ventricular pressure variations may be secondary to abnormalities of right ventricular function, presumably because of disordered right ventricular activation sequence.

Stimulation of Renin Secretion by Hydralazine: I. Studies in Experimental Hypertension of Coarctation of the Aorta

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The effect of hydralazine was studied on renin secretion in normal and surgically coarcted dogs. Renin activity was determined by rat bioassay in the peripheral and renal venous plasma. Immediately following surgical coarctation of the thoracic aorta, plasma renin activity increased and reached a maximal level in 24 to 48 hours. These changes in renin activity were associated with a marked fall in the mean blood pressure and pulse pressure distal to the coarctation and a rise in the blood pressure proximal to the coarctation. In one to two weeks after surgery, the plasma renin activity had returned to control levels, even though the blood pressure proximal to the coarctation had risen to severe hypertensive levels. At this time the mean blood pressure distal to the coarctation had returned to control levels, whereas the pulse pressure had remained low. Hydralazine, when injected intravenously into coarcted dogs whose renin activity had returned to normal, caused a marked increase in plasma renin activity. In normal control dogs intravenous hydralazine caused little or no increase in plasma renin activity. Intravenous pentolinium, which produced a fall in blood pressure comparable with that of hydralazine, did not increase renin activity in the control and coarcted dogs. The beta adrenergic blocking agent, propranolol, and intravenous reserpine also did not alter renin activity in the control and coarcted dogs. These findings suggest that renin secretion is stimulated by hy-

dralazine in hypertensive dogs with a reduced pulse pressure. Intravenous hydralazine may prove to be a test for hypertension caused by altered renal function.

Effect of Microphone Position on Systolic Configuration of Apexcardiogram

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Changes in the systolic wave patterns of the apexcardiogram were studied in relation to changes in recording site in nine patients with rheumatic heart disease. A systematic recording of the apexcardiogram at multiple sites (as many as 40 in the same individual) about the apex invariably revealed the following: While the diastolic waves changed little within a certain range of microphone positioning, a late systolic bulge was produced with medial displacement of the microphone and a mid-systolic bulge with lateral displacement. These findings would indicate nonspecificity of these systolic waves which have been considered to be pathognomonic of hypertrophic subaortic stenosis.

Standardization of the means of obtaining an apexcardiogram seems necessary in view of the inconsistency in the systolic wave patterns resulting from minimal displacement of the microphone away from the point of maximal impulse, the determination of which is rather subjective. It is proposed that the tracing with the smoothest excursion of the systolic waves be selected.

Possible Role of Unilateral Changes in Sympathetic Tone in the Production of Neurogenic Electrocardiographic Abnormalities (P)

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Although patients with central nervous system disorders often have abnormal electrocardiograms in the absence of known organic heart disease, little is known of the precise electrophysiological mechanisms responsible for these abnormalities. It is possible that altered sympathetic tone, producing localized refractory period changes in the ventricular myocardium, might account for some of these electrocardiographic abnormalities.

Lead II electrocardiograms were recorded and studied following procedures which altered sympathetic tone in the open-chest, barbiturate-anesthetized dog preparation. Unilateral stellate ganglionectomy and stimulation produced consistent electrocardiographic changes in 48 dogs. Right stellate ganglionectomy with intact left stellate or left stellate stimulation resulted in T waves of increased area and prolonged QT intervals in 45 of 45 dogs. Left stellate ganglionectomy with an intact right stellate or right stellate stimulation produced a significant depression or inversion of the T wave in 14 of 35 dogs.

Ventricular refractory period changes following unilateral stellate ganglionectomy were measured at each of 16 test points in 24 dogs. Right stellate ganglionectomy resulted in refractory period prolongation on the anterior surface of the ventricles, and left stellate ganglionectomy produced similar prolongation on the posterior left ventricle surface.

It is concluded that alterations in sympathetic tone to the ventricles in dogs can result in predictable electrocardiographic changes, and these changes may be due in part to an altered ventricular gradient caused by local changes in the ventricular refractory period. The electrocardiographic changes noted in these experiments are similar to those reported in man with central nervous system disorders.

Elevation of Serum Lactic Dehydrogenase in Medical and Surgical Cardiac Patients Without Acute Myocardial Damage

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Activity of total lactic dehydrogenase (LDH) and that of the heat-stable ("myocardial") isozyme was measured in the serum of cardiac patients with congenital and valvular heart disease before and after cardiac catheterization and after cardiac surgery. No patients were acutely ill, although most were symptomatic. Of nine patients with ball-valve prostheses, all had elevations in both heat-stable and total LDH activity three to 36 months after operation, although all had greatly improved symptomatically and/or hemodynamically. Of the eight postoperative patients who did not have prosthetic ball valves, six had normal activities 12 or more months after operation. These patients had little or no remaining hemodynamic abnormalities at catheterization. The two postoperative patients with increased LDH activity still had gross residual hemodynamic abnormalities.

Of 20 consecutive patients studied before cardiac catheterization, only nine had normal total and heat-stable activity; five had elevation of heat-stable and total activity, and six had elevation of total activity only. Of the 15 patients with normal heat-stable LDH activity before catheterization, four had abnormally high activity immediately after the procedure. Four of the five patients with elevated heat-stable activity

before catheterization showed significantly greater activity afterward. In no case was there other corroborating evidence of myocardial damage, although in one case there was an episode of hypotension and ventricular irritability. It would seem that the precise significance of increased heat-stable LDH activity deserves further investigation.

Effect of Monoamine Oxidase Inhibition on the Metabolism of Norepinephrine by the Isolated Rat Liver (P)

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We have used the isolated rat liver perfusion system to study the effect of monoamine oxidase (MAO) inhibitors on the metabolism of *dl* and *l*-norepinephrine-8-^{14}C (NE). Approximately 5 to 10 μg of *dl* or *l*-NE-^{14}C were added to the perfusate; blood and bile flow remained normal in all experiments. Plasma and bile were collected at intervals, and the distribution of ^{14}C in free NE and in its metabolites was studied with a liquid scintillation counter. Free NE was isolated on an alumina column by a modification of the Weil-Malherbe and Bone procedure, and paper chromatographic methods were used to separate the metabolites. Control studies revealed clearance of plasma of free NE in the first hour to less than 10% of the dose of ^{14}C. In five hours 30% of ^{14}C was excreted in the bile as the sulfate of 3-methoxy-4-hydroxyphenylglycol (MHPG) and the glucuronide of normetanephrine (NMET). Oxidative deamination of NE with formation of MHPG proceeded normally when pargyline was added to the perfusate (1 to 50 mg/120 ml). Pretreatment of liver donors with pargyline (30 to 50 mg/kg/day) resulted in MAO inhibition, indicated by an increase in urinary tryptamine and, in the liver perfusion, by a decrease in MHPG production and a decreased clearance of NE from the plasma. Addition of 1 to 2 mg of β-phenylisopropylhydrazine (JB516) to the perfusate markedly suppressed MHPG production in the first hour of perfusion; radioactivity in the bile and clearance of plasma of free NE were unaltered. Thus, in the isolated liver system, inhibition of NE metabolism can be produced directly by JB516 or indirectly by pretreatment of liver donors with pargyline.

Exploratory Pericardiectomy in the Diagnosis and Treatment of Problem Cases with Congestive Failure or Recurrent Chest Pain

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Two patterns of pericarditis occur where diagnosis is sometimes impossible: (1) chronic congestive failure requires differentiation between pericarditis and myocardiopathy and (2) recurrent chest pain can represent pericarditis or ischemic heart disease. We believe exploratory pericardiectomy is indicated when the diagnosis remains uncertain.

Within 18 months 356 patients were studied by right- and left-heart catheterization plus selective cineangiography; 174 had valvular, 112 congenital, and 70 coronary heart disease, myocardiopathy, or pericarditis.

Chronic congestive failure was a diagnostic problem in 37 patients. Twenty-three had myocardiopathy: six diagnosed by autopsy, 14 by special studies, and three clinically. Eight had severe coronary disease, five diagnosed by cineangiography and three at autopsy. Two had classic constrictive pericarditis. In four the diagnosis was unclear, and exploratory pericardiectomy was performed. Two had pericarditis with marked improvement following operation. One with slight pericarditis died 14 months later of progressive myocardiopathy. One without pericarditis died eight months later of primary pulmonary vascular disease.

Ten patients had recurrent chest pain and nonspecific electrocardiographic changes. Recurrent idiopathic pericarditis was diagnosed in six, and pericardiectomy produced complete relief. Two others showed significant coronary disease on cineangiography. The diagnosis was uncertain in two. Exploratory thoracotomy was performed and thickened pericardium removed. One was markedly improved; the other was completely relieved.

These observations suggest that pericardiectomy should be considered for diagnosis and treatment when pericarditis cannot be ruled out. Four of six patients so treated were markedly improved.

INDEX OF AUTHORS

A

Abboud, F. M. II-189
Abelman, W. H. II-41
Abildskov, J. A. II-41, 61, 151, 222, 223
Ablaza, S. II-162
Achor, R. W. P. II-13
Adam, A. II-162
Adams, M. L. II-111
Adams, P., Jr. II-120, 174
Ades, F. II-41
Adwers, J. R. II-120
Aggeler, P. M. II-166
Ahmed, S. II-129
Aktin, E. II-1
Alaupovic, P. II-25
Alexander, N. II-41
Alexander, S. II-42
Alfin-Slater, R. B. II-1
Allard, C. II-27
Allen, D. F. II-131
Allen, E. J. II-161
Altman, S. II-60
Anagnostopoulos, C. E. II-42
Anderson, B., Jr. II-185
Anderson, G. J. II-43
Anderson, P. A. W. II-85
Anderson, R. C. II-120
Anderson, R. W. II-213
Andrews, H. G. II-125
Angelakos, E. T. II-43
Angell, W. W. II-139
Angrist, A. A. II-159
Ankeney, J. L. II-56, 68
Anstadt, G. L. II-43
Antia, A. U. II-44
Antonius, N. A. II-57, 167
Arbulu, A. II-44
Arevalo, F. R. II-109
Armstrong, M. L. II-84
Asdel, A. K. II-22
Ashford, T. P. II-30
Asli, R. P. II-53
Asperger, Z. II-44
Auchincloss, J. H., Jr. II-97
Austen, W. G. II-108, 186, 187
Austin, D. J. II-207
Awai, K. II-111
Ayres, S. M. II-96

B

Bajusz, E. II-45, 174
Baker, J. B. II-131
Baker, J. R. II-45
Baker, S. P. II-1
Balla, G. A. II-210
Ballinger, W. F., II II-98
Barbour, A. M. II-45
Barbour, B. H. II-45
Barner, H. B. II-188
Baron, R. H. II-219
Barrett, J. S. II-120
Bartle, S. H. II-45
Bashour, F. A. II-46
Bassett, D. R. II-2
Baue, A. E. II-43, 224
Baule, G. II-97
Baxley, W. A. II-46, 109
Bazika, V. II-70
Beall, A. C. II-70
Beeson, J. R. II-46
Beheler, E. M. II-68
Bell, P. II-35
Bellas, A. E. II-194
Bellet, S. II-12, 19, 29, 123, 206, 218
Benchimol, A. II-47
Bender, S. R. II-129
Bennett, L. II-190
Bennett, R. S. II-21
Benson, D. W. II-157
Benson, H. II-198
Bentivoglio, L. G. II-48, 180, 223
Berg, H. F. II-23
Berge, K. G. II-13
Berger, M. II-130
Berger, V. II-31
Bergner, L. II-48
Bergstedt, R. G. II-62
Berkovits, B. II-65
Berkowitz, D. II-2
Berman, H. J. II-48,191
Bernhard, W. F. II-49
Bernstein, A. II-49
Bernstein, H. II-70
Bernstein, I. J. II-49
Bernstein, S. II-122
Bernstein, W. H. II-186
Berry, J. II-142
Best, M. M. II-10
Beteta, E. II-50
Bianchi, F. A. II-218
Biddle, M. II-122
Bierenbaum, M. L. II-3, 12
Biern, R. O. II-90
Bilgutay, A. M. II-50
Bilitch, M. II-132
Bing, R. J. II-102
Birbari, A. E. II-50, 200
Birtwell, W. C. II-51, 113
Bistue, A. R. II-218
Black, A. II-3
Black, M. M. II-3
Black, W. L. II-51, 52
Blackaller, J. II-172
Blackburn, H. W. II-33
Blake, T. M. II-119
Blakemore, W. S. II-43, 224
Blanco, G. II-162
Bloch, J. H. II-52
Bloom, W. L. II-52
Bloor, B. M. II-53
Bloor, C. M. II-53
Blount, S. G., Jr. II-150, 166, 212, 221
Blumenthal, M. R. II-148
Blumenthal, S. II-62
Bogdonoff, M. D. II-53
Boicourt, O. W. II-54
Boineau, J. P. II-54
Bokkenheuser, V. D. II-114
Bond, T. P. II-54
Bonnabeau, R. C., Jr. II-138
Booth, R. W. II-64, 136, 145, 183
Bor, I. II-59
Borun, E. R. II-55
Bostock, B. A. II-55
Boswell, J. II-103
Botti, R. E. II-56
Botticelli, J. T. II-56
Bourianoff, G. G. II-82
Bowers, D. L. II-173
Boyle, E., Jr. II-4
Boyle, E. C. II-7
Boyles, P. W. II-4
Brachfeld, N. II-56
Bradford, R. H. II-8
Bradham, R. R. II-184
Bradley, E. C. II-57
Brady, A. J. II-130
Brancato, R. W. II-57, 167
Braunwald, E. II-58, 71, 91, 127, 145, 179, 200, 220
Braunwald, N. S. II-58, 205
Brawley, R. K. II-211
Brennan, J. C. II-189
Brest, A. N. II-129, 166, 199, 204
Briggs, L. S. II-65
Bristow, J. D. II-54, 58, 127, 137
Broadbent, J. C. II-63
Brodeur, M. T. H. II-58
Bromberger-Barnea, B. II-59
Brooks, H. II-100
Brooks, R. H. II-107
Brown, D. F. II-59
Brown, D. W. II-150
Brown, G. C. II-59

Brown, H. B. II-4
Brown, I. W., Jr. II-218
Brown, J. G. II-33
Brown, K. W. G. II-141
Brown, M. II-33
Bruce, R. A. II-60, 145, 156, 183
Brunner, D. II-60
Brusco, O. J. II-5
Buchwald, H. II-60
Buckley, N. II-100
Budow, J. II-61
Buerger, W. E. II-92
Bullivant, S. II-153
Burch, G. E. II-61
Burgess, M. J. II-61
Burkhalter, L. II-143
Burlando, A. II-110
Burnett, W. F. II-134
Burns, R. B. P. II-148
Burns, W. H. II-46, 62
Burris, J. II-62
Bursch, J. H. II-110
Butkus, A. II-5, 27
Buxton, R. W. II-85

C

Cade, R. II-135
Cafferky, E. II-132
Cagirgan, C. M. II-216
Cahill, J. L. II-62
Cain, C. II-53
Calatayud, J. B. II-63
Caldwell, A. B. II-3
Caldwell, J. R. II-213
Call, E. P. II-146
Callahan, J. A. II-63
Calloway, J. H. II-203
Camishion, R. C. II-155
Canent, R. V., Jr. II-85
Canete, D. R. II-57, 167
Cannon, J. A. II-198
Cannon, P. J. II-63
Capp, M. P. II-143
Caravaca, J. II-64
Carleton, R. A. II-64
Carliner, N. H. II-184
Carnazzo, A. J. II-64
Carr, J. G. II-49
Carr, P. W. II-157
Castaneda, A. R. II-65
Castellanos, A., Jr. II-65
Castle, C. H. II-65
Castle, R. F. II-66
Center, S. II-66
Cestero, J. II-143
Chaffee, W. R. II-66
Chang, J. C. II-143
Chapman, J. M. II-55
Chardack, W. M. II-67, 92
Chattopadhyay, D. P. II-114
Cheng, T. O. II-67
Chesney, J. G. II-131
Chidsey, C. A. II-200
Cho, Y. W. II-19, 206
Chobanian, A. V. II-18
Choi, J. II-5, 17
Choi, S. S. II-13
Chou, C. II-206
Cingolani, H. E. II-67
Clarke, G. B. II-6
Clarkson, T. B. II-6, 22
Co, B. S. II-103
Cobb, L. A. II-163
Coffin, L. H., Jr. II-68
Coffman, J. D. II-68
Cohen, L. II-6
Cohn, J. N. II-69
Cohn, L. J. II-77, 89, 130
Collens, W. S. II-7
Collins, H. A. II-69
Collins, J. A. II-200
Comroe, J. H., Jr. II-39
Conley, T. L. II-35
Conn, R. D. II-145, 183
Connor, W. E. II-18
Conrad, M. C. II-69
Conrad, P. W. II-117
Coodley, E. L. II-70
Cook, W. A. II-216
Cooke, R. E. II-44
Cooley, D. A. II-70
Cooper, E. E. II-7
Cooper, G. R. II-7, 20
Cooper, J. II-181
Cooper, T. II-121, 200
Corday, E. II-70
Corrin, K. II-218
Cosby, R. S. II-132
Cotton, E. K. II-70
Covell, J. W. II-71, 145
Cox, R. II-197
Crank, R. P., Jr. II-7, 20
Crawford, E. W. II-154
Creech, O., Jr. II-170
Crevasse, L. II-71
Crider, Q. E. II-8
Criley, J. M. II-71, 117, 219
Criscitiello, M. G. II-72
Cristofalo, V. J. II-170
Cronin, R. F. P. II-72
Cross, F. S. II-72
Cruz, A. II-103
Cuccia, C. II-143
Cuddy, R. P. II-80
Culp, D. A. II-125
Curreri, P. W. II-8, 152
Currier, R. D. II-98

D

Dabney, J. M. II-74
Daddario, R. C. II-69
Dadmun, S. II-172
Daicoff, G. R. II-73
Dalen, J. E. II-73
Damato, A. N. II-139
Dammann, J. F., Jr. II-45
Daniel, R. A., Jr. II-69
Daniels, J. B. II-43
Danilowicz, D. II-74, 113
Daoud, A. S. II-30
Dapena, A. V. II-161
Darby, T. D. II-207
Daugherty, R. M., Jr. II-74
David, N. J. II-74
David, P. R. II-75
Davies, A. L. II-155
Davila, J. C. II-75
Davis, H. L. II-8
Davis, J. H. II-129
Dawber, T. R. II-121
Day, A. J. II-9
Dayton, S. II-9
DeBakey, M. E. II-33
de la Cruz, Ma. V. II-75
DeLaurentis, D. A. II-75, 210
de Leon, A. C., Jr. II-76, 108
Demartini, F. E. II-63
DePasquale, N. P. II-61
Derrick, J. R. II-54, 201
DeSanctis, R. W. II-186
Deterling, R. A., Jr. II-51, 194, 200
Deutscher, S. II-10
DeWeese, J. II-188
Dexter, L. II-73, 202
Deykin, D. II-30
Dimond, E. G. II-47, 64
Dixon, H. B., II II-83
Di Giorgi, S. II-3
Djordjevich, J. II-6
Dobkin, G. B. II-7
Dodds, R. P., Jr. II-216
Dodge, H. T. II-109
Doherty, J. E. II-76
Donoso, E. II-77, 89
Dontas, A. S. II-17
Dotter, C. T. II-77
Dowell, A. R. II-124
Downing, S. E. II-78
Doyle, E. F. II-78
Doyle, J. T. II-59
Drake, R. P. II-108
Dreifus, L. S. II-78, 187
Dressler, W. II-79
Driscoll, J. F. II-208
Droste, H. H. II-162
Ducore, D. J. II-203
Dugge, J. E. II-19
Dumanian, A. V. II-168
Duncan, C. H. II-10
Dunlap, W. M. II-154
Durrer, D. II-79, 140, 163
DuShane, J. W. II-84
Dustan, H. P. II-90
Dvornik, D. II-10
Dyer, J. II-79, 80, 205
Dyrda, I. II-20

E

Earle, D. P. II-197
Eastwood, G. L. II-89
Eckstein, J. W. II-189
Edmonds, J. H., Jr. II-175
Edmonson, R. E. II-46
Edmundowicz, A. C. II-80

Edwards, E. A. II-62
Edwards, J. E. II-13, 91, 93, 142, 174, 197, 215
Edwards, M. L. II-171, 202
Ehrlich, E. W. II-148
Eich, R. H. II-19, 41, 66, 80, 222
Eisenberg, H. II-115
Eisenberg, L. II-42
Eisenberg, S. II-81
Elias, R. A. II-24
Eliasch, H. II-81
Eliot, R. S. II-82, 152
Elliott, W. C. II-111, 204
Ellis, F. H., Jr. II-63
Ellis, J. G. II-47
Ellison, L. T. II-103
Ellison, R. G. II-103
Engelberg, H. II-11
Engelman, K. II-82
Engler, L. F. II-4
Entman, M. L. II-82, 83, 171
Epstein, F. H. II-10
Ertel, P. Y. II-203
Escher, D. J. W. II-198
Estes, E. H., Jr. II-83, 154
Evans, J. R. II-29
Ewy, G. A. II-83

F

Fabrykant, M. II-95
Fahrenbach, M. J. II-11
Fallon, K. II-191
Farrand, M. E. II-4
Federico, A. J. II-67, 92
Feil, G. H. II-110
Feinberg, L. J. II-12, 29, 123
Feinstein, A. R. II-83
Feldt, R. H. II-84
Felts, J. M. II-101
Fenton, J. II-102
Fetner, J. E. II-7, 20
Fidge, N. H. II-9
Fiene, T. J. II-84
Figley, M. M. II-104
Fine, G. II-118
Finney, J. W. II-210
Fishman, A. P. II-99
Fitz, A. E. II-84, 125
FitzPatrick, M. II-12
Flaherty, J. T. II-85
Flanigan, W. J. II-76
Fleischman, A. I. II-3, 12
Flock, E. V. II-195, 224
Florin, A. II-3
Flotte, C. T. II-85
Flowers, N. C. II-116
Floyd, W. L. II-85, 174
Folger, G. M., Jr. II-182
Forbath, N. II-29
Forman, D. T. II-13
Forman, H. II-164
Forwand, S. A. II-86
Foster, J. H. II-86
Foulk, C. R. II-105
Fowler, N. O. II-87, 115
Fox, M. II-129
Frahm, C. J. II-215
Frank, C. W. II-87
Frank, M. J. II-87, 136
Frankl, W. S. II-88
Frantz, I. D., Jr. II-23
Frazier, L. E. II-88, 96, 220
Freeman, L. II-23
Fregly, M. J. II-88
Frei, E. II-161
Freud, G. II-79
Friedberg, C. K. II-77, 89, 131
Friedberg, S. J. II-133
Friedenberg, M. J. II-168
Friedman, E. H. II-89
Friedman, R. H. II-88
Friesinger, G. C. II-90, 98
Frische, L. H. II-77
Frohlich, E. D. II-90
Frohnert, P. P. II-90
From, A. H. L. II-91, 215
Frommer, P. L. II-91
Frost, A. II-142
Fry, D. L. II-169
Frye, R. L. II-95
Fujita, T. II-31
Fukuba, H. II-1
Fuller, H., Jr. II-91
Furman, R. H. II-5, 8
Furman, S. II-198
Fuson, R. L. II-92

G

Gaal, P. G. II-98
Gabor, J. B. II-54
Gadboys, H. L. II-92, 100, 214
Gage, A. A. II-67, 92
Gallie, T. M. II-54
Gamble, W. J. II-93, 153
Gamboa, R. II-79, 117, 153
Gannon, P. G. II-93
Garber, M. M. II-14
Gardner, D. L. II-94
Gardner, T. H. II-78
Garelick, H. II-98
Garland, L. II-142
Garon, L. P. II-48
Garrison, G. E. II-128
Garzon, A. A. II-94
Gass, J. D. II-74
Gault, J. H. II-94
Gauthier, G. II-170
Gazzaniga, A. B. II-177
Gearing, F. R. II-48
Gedge, S. W. II-13
Geer, J. C. II-13
Gelfand, M. L. II-14, 95
Geller, E. II-123
Gensini, G. G. II-3
Gentsch, T. O. II-131
Geraci, J. E. II-95
Gerber, C. J. II-149
Gerbode, F. L. II-104, 113, 177, 191, 192
Gertler, M. M. II-95
Getz, G. S. II-88, 96, 220
Giannelli, S., Jr. II-96
Gibas, M. A. II-82
Gibson, T. C. II-96
Gifford, R. W., Jr. II-97
Gilbert, R. II-97
Gillespie, J. F. II-117
Gilmore, J. P. II-67
Gilson, A. J. II-212
Ginn, W. M., Jr. II-97, 128
Giragos, H. G. II-168, 215
Giron, F. II-51, 200
Gitlow, S. E. II-221
Givner, M. L. II-10
Glasgow, J. L. II-98
Glassman, S. II-2
Glenn, W. W. L. II-42, 146
Glynn, M. F. II-25
Gold, H. II-70
Goldberg, B. II-170
Goldberg, H. II-35, 48, 63, 173, 180, 223
Goldfarb, D. II-98
Goldman, A. G. II-98
Goldman, H. S. II-99
Goldring, D. II-112
Gomez, L. II-83
Gonzalez, I. E. II-14
Gonzales, N. II-80
Goobar, J. T. II-196
Goodkind, M. J. II-99
Goodman, B. II-100
Goodman, M. L. II-14
Goodrich, J. K. II-98
Goodwin, R. S. II-135, 199
Goodyer, A. V. N. II-100
Goor, D. II-161
Gootman, N. L. II-100
Gore, I. II-14, 20
Gorlin, R. II-111, 126, 146, 204
Gorman, P. A. II-63
Gotoh, F. II-151
Gott, V. L. II-185
Gould, R. G. II-15, 31
Gousios, A. G. II-101
Graettinger, J. S. II-64
Graupner, K. I. II-179
Greatbatch, W. II-67, 92
Green, D. P. II-3
Green, E. II-60
Green, G. E. II-101
Greenburg, A. G. II-73
Greene, L. F. II-209
Greenfield, B. M. II-178
Greenhouse, A. H. II-101
Gregoratos, G. II-23
Griffin, J. R. II-84
Griggs, D. M., Jr. II-102, 164
Griswold, H. E. II-54, 58, 127, 137, 172, 202
Grondin, C. M. II-142
Gronkowski, L. A. II-159
Groover, M. E., Jr. II-15
Gross, R. E. II-177
Grossman, L. M. II-1

Grove, G. R. II-216
Grover, R. F. II-102
Gudbjarnason, S. II-102
Guest, J. L., Jr. II-103
Guest, M. M. II-54
Gulotta, S. J. II-181
Gunn, C. G. II-103
Gunnar, R. M. II-49, 103, 172, 208
Guntheroth, W. G. II-104, 154
Gurewich, V. II-104, 207
Gutstein, W. H. II-190
Guzman, M. II-116

H

Haber, E. II-167
Hackel, A. II-104
Hackel, D. B. II-82, 83, 143
Haddy, F. J. II-74
Haft, J. I. II-131
Hagopian, M. II-16,17
Hait, G. II-105, 183
Hale, A. R. II-61
Halkett, J. II-191
Hallman, G. L. II-70
Hamby, R. I. II-130
Hames, C. G. II-105, 198
Hamlin, R. L. II-105
Hanlon, C. R. II-121
Hansen, J. E. II-106
Hardin, C. A. II-106
Harken, D. E. II-202
Harman, D. II-16
Harman, M. A. II-106
Harris, C. W. II-85, 106
Harris, W. S. II-107
Harrison, D. C. II-84, 108
Harrison, J. H. II-113
Harthorne, J. W. II-108, 186
Harumi, K. II-61
Harvey, W. P. II-108, 109
Hashimoto, S. II-9
Hastreiter, A. R. II-109
Hatch, F. T. II-17
Hauser, S. II-31
Haust, M. D. II-5, 17
Havel, R. J. II-101
Hawley, R. R. II-46, 109
Hayashi, Y. II-211
Haynes, F. W. II-73
Hayton, T. II-12
Haywood, J. II-110
Heider, C. H. II-166
Heider, J. G. II-11
Heintzen, P. H. II-110
Held, K. II-162, 188
Hellems, H. K. II-217
Hellerstein, H. K. II-89, 110
Hellman, L. II-28
Helmsworth, J. A. II-115
Hennes, A. R. II-111
Henney, R. P. II-211
Herman, M. V. II-111
Hernandez, A., Jr. II-112
Hernandez, H. J. II-1
Herr, R. H. II-202
Herron, R. E. II-17
Hessel, E. A., II II-112
Hetenyi, G., Jr. II-29
Hewitt, R. II-170
Heyman, A. II-133, 185
Heymann, M. II-100, 183
Hickler, R. B. II-50, 113
Higgs, R. W. II-178
Hightower, B. M. II-113
Hill, J. II-45
Hill, J. D. II-113
Hinman, A. II-32
Hirsch, E. Z. II-110
Hoak, J. C. II-18
Hoffman, B. F. II-165,197
Hoffman, J. I. E. II-74, 113
Hofmann, A. F. II-114
Holcomb, W. II-42
Holland, P. II-114
Hollander, W. II-18, 20, 118, 222
Holmberg, G. II-115
Holmes, J. C. II-87, 115
Holtzman, C. M. II-28
Hombein, T. F. II-154
Homburger, F. II-45
Honeyman, M. S. II-115
Honigman, F. M. II-161
Hoobler, S. W. II-116
Horan, L. G. II-116
Horlick, L. II-18
Horwitz, D. II-82
Hosier, D. M. II-221
Hospelhorn, V. D. II-12
Hovig, T. II-19
Howard, J. M. II-152
Howard, R. P. II-5
Huang, T. II-149
Hubis, H. J. II-116
Hudson, H. L. II-168
Hufnagel, C. A. II-108, 117
Hugenholtz, P. G. II-93, 117
Hughes, R. H. II-96, 220
Hultgren, H. N. II-116
Humphries, J. O. II-117
Hunt, J. C. II-209
Hunt, O. R., Jr. II-189
Hurlburt, J. C. II-85
Hurst, J. W. II-169
Hutchins, G. M. II-150, 182
Huvos, A. II-118

I

Indeglia, R. A. II-65
Inoue, G. II-20, 222
Inoue, T. II-169
Irons, G. V., Jr. II-97, 128
Ishigura, J. II-131

J

Jackson, J. C. II-111
Jacobs, W. H. II-118
Jagger, P. I. II-132
Jain, S. II-6, 26
James, L. R. II-8
James, T. N. II-118
Janeway, R. II-69
Jarman, J. B. II-5
Jelinek, G. N. II-119
Jelliffe, R. W. II-119
Jenkins, A. C. II-210
Jesse, M. J. II-62
Jimenez, J. II-123
Johnson, A. S. II-215
Johnson, B. S. II-170
Johnson, D. II-65
Johnson, E. E. II-196
Johnson, R. II-162
Johnson, R. A. II-119
Jonas, S. II-79, 83
Jones, J. R. II-120
Jones, R. II-21
Jones, R. D. II-72
Jones, S. E. II-89
Jordan, G. L., Jr. II-33
Jordan, J. W., Jr. II-60, 147
Jorgensen, C. R. II-203
Jorgensen, L. II-19
Joyner, C. R., Jr. II-120
Jude, J. R. II-212
Judge, R. D. II-157, 173, 196
Judkins, M. P. II-77
Jue, K. L. II-91, 120, 174

K

Kahn, M. II-92, 100
Kahn, O. II-141
Kain, H. II-32
Kaiser, G. C. II-121
Kakimi, R. II-151
Kako, K. K. II-121
Kanjuh, V. I. II-93
Kannel, W. B. II-121
Kapadia, G. G. II-143
Kapany, N. S. II-108
Kardatzke, M. L. II-158
Karlson, K. E. II-94, 140
Karow, A. M., Jr. II-216
Kartchner, M. M. II-207
Karvonen, M. J. II-17
Kashemsant, U. II-19, 80
Kaspar, A. J. II-44, 164
Kasparian, H. II-164
Kattus, A. A. II-122
Katz, L. N. II-26
Kay, J. H. II-122
Keech, M. K. II-218
Keighley, J. F. II-66
Kelly, G. J. II-64
Kelly, J. J. II-191, 192
Kelly, P. B., Jr. II-180
Kelminson, L. II-70
Kennedy, J. W. II-112
Kershbaum, A. II-19, 123
Kerth, W. J. II-191, 192
Keyes, F. P. II-8, 152
Keys, A. II-17, 33
Kezdi, P. II-123
Khalil, H. H. II-124

Kidd, L. II-124, 193, 194
Kilburn, K. H. II-124
Killen, D. A. II-86
Killip, T. II-125
Kim, D. N. II-21
Kincaid, O. W. II-63
Kinch, S. H. II-59
King, H. II-125
King, M. II-43
Kingsley, B. II-44, 191
Kirkendall, W. M. II-84, 125
Kirklin, J. W. II-113
Kissil, D. II-170, 220
Kjelsberg, M. O. II-10
Klainer, L. II-96
Klassen, G. A. II-126
Klatte, E. C. II-86
Klein, G. C. II-7, 20
Klein, M. D. II-111, 126, 146
Kleinfeld, M. II-126
Kline, H. J. II-130, 143
Klocke, F. J. II-127, 220
Kloster, F. E. II-58, 127, 172
Knopp, T. J. II-75, 128
Kochwa, S. II-92
Kok-Ewe, C. II-56
Koler, R. D. II-58
Koletsky, S. II-128
Kong, Y.-H. II-128
Kontos, H. A. II-179
Koroxenidis, G. T. II-155
Kosek, J. C. II-139
Kositchek, R. J. II-129
Kosowsky, B. D. II-139
Koss, L. G. II-160
Kottke, B. A. II-130
Kowitz, P. E. II-166
Kramsch, D. M. II-20, 222
Krasnow, N. II-129
Krivit, W. II-215
Kroman, H. S. II-129
Kroop, I. G. II-61
Kropatkin, M. II-166
Kubota, M. II-31
Kuether, F. W. II-178
Kuhn, L. A. II-130, 143
Kuo, P. T. II-21
Kuttner, A. G. II-78
Kyle, R. A. II-130

L

LaDue, J. S. II-148, 160
LaFarge, C. G. II-93
Lagg, S. II-167
Laing, C. P. II-94
Lalich, J. J. II-211
Lane, F. J. II-126
Lang, T.-W. II-70
Lange, R. L. II-56
Langendorf, R. II-135
Langer, G. A. II-130
Langford, H. G. II-215
Laragh, J. H. II-63
Larson, S. J. II-131
Lary, B. G. II-131
Lasser, R. P. II-131, 132
Lau, F. Y. K. II-132
Lau, S. H. II-139
Lauler, D. P. II-113, 132, 133
Laureta, H. C. II-206
Lawrence, M. S. II-125
Lazzara, R. II-197
Leathers, J. E. II-177
LeBauer, J. E. II-133
LeBeau, R. J. II-27
Ledbetter, M. K. II-134
Lee, G. B. II-144
Lee, K. T. II-21
Lee, W. H., Jr. II-184
Leeds, R. II-177
Lefcoe, N. M. II-176
Lefemine, A. A. II-134
Lefer, A. M. II-134
Leffler, W. B. II-135
Lehan, P. H. II-106, 155
Leibinsohn, S. II-161
Leighton, R. F. II-135
Leland, O. S., Jr. II-187
Lemberg, L. II-65
Lemmon, W. M. II-166
Leon, A. S. II-53
Leong, L. S. II-166
Lev, M. II-135
Levi, L. II-115
Levin, A. R. II-85
Levin, D. M. II-135
Levin, H. S. II-64, 136, 145, 183
Levin, S. II-44
Levine, H. D. II-136, 146
Levine, H. J. II-86
Levine, R. S. II-129
Levinson, G. E. II-87, 136
Levitt, M. II-83
Lewis, J. II-133
Lewis, K. B. II-71, 117, 219
Lewis, R. P. II-137
Libanoff, A. J. II-137
Licata, R. II-105
Lichtman, M. A. II-105
Lieberman, J. S. II-138
Liggett, M. S. II-47
Likar, I. II-90
Likar, I. N. II-21, 22
Likar, L. J. II-21, 22
Likoff, W. II-191
Lillehei, C. W. II-50, 93, 138, 142
Lillehei, R. C. II-52
Lillenstein, M. II-189
Lim, M. T. II-208
Lim, S. T. II-144
Lin, B. J. II-29
Lindner, M. II-138
Linenthal, A. J. II-138
Linhart, J. W. II-139
Lintermans, J. P. II-104
Lipana, J. G. II-102
Lister, J. W. II-139
Litwak, R. S. II-92, 100, 214
Loebl, K. II-60
Lofland, H. B., Jr. II-6, 22
Lombardo, C. R. II-212
Lopez, A. II-186
Losada, M. II-170, 220
Lotti, L. II-182
Loubier, R. J. II-62
Lourie, I. N. II-11
Love, W. D. II-141
Lower, R. R. II-139
Lucardie, S. M. II-140
Lynfield, J. II-140
Lyon, D. II-141

M

MacDonald, W. J. II-178
MacAlpin, R. N. II-122
MacMillan, R. L. II-141
MacNintch, J. E. II-22
Maher, F. C. II-209
Main, F. B. II-113
Majzoub, H. S. II-53
Malinow, M. R. II-141, 144
Mallam, J. T. II-210
Malm, J. R. II-62
Manalo-Estrella, P. II-22
Mandelbaum, I. II-142
Mann, G. II-142
Mannick, J. A. II-68, 118
Mantini, E. L. II-142
Maranhao, V. II-63
Marano, A. J., Jr. II-130, 143
Marcus, F. I. II-83, 143
Marcus, H. S. II-199
Margolis, N. II-110
Marik, S. II-110
Markov, A. K. II-106
Markowitz, M. II-78
Marshall, R. J. II-80, 118
Marsten, J. L. II-56
Marticorena, E. II-79
Martin, A. M., Jr. II-82, 143
Martin, R. H. II-144
Martin, W. E. II-154
Martt, J. M. II-144
Maruffo, C. A. II-141, 144
Marx, H. J. II-145, 183
Mason, D. II-148
Mason, D. T. II-94, 145
Mason, R. E. II-90
Massell, B. F. II-153
Massey, F. J. II-55
Massie, H. L. II-187
Massih, N. A. II-145
Massumi, R. A. II-146
Master, A. M. II-132
Matano, I. II-146
Mathé, A. II-115
Mathur, V. S. II-73, 146
Mauney, F. M. II-218
Mauro, A. II-42
Maxwell, R. A. II-147
Mazer, E. II-29
Mazzarella, J. A. II-60, 147, 156
McConahey, W. M. II-91
McCool, D. C. II-148
McCord, C. W. II-58, 127
McCormack, L. J. II-97

McCutcheon, E. P. II-184
McDade, B. G. II-148
McDaniel, D. B. II-141
McDermott, P. H. II-145
McDonald, I. G. II-167
McDonald, R. H., Jr. II-67
McDonough, J. R. II-105, 198
McEachen, J. A. II-129, 198
McEwen, C. II-176
McGarvey, J. F. X. II-148
McGiff, J. C. II-148
McGough, G. A. II-104
McGregor, M. II-159
McIntosh, H. D. II-149, 154, 171, 216, 218
McIntyre, K. M. II-86
McKusick, V. A. II-149
McLean, C. E. II-171
McNamara, P. M. II-121
Medearis, D. N., Jr. II-150
Medow, A. II-159
Meek, D. C. II-150
Mehrizi, A. II-150, 182
Meijler, F. L. II-79, 163
Meilman, E. II-28
Mendel, J. G. II-150
Mendenhall, J. T. II-185
Mendlowitz, M. II-221
Meng, H. C. II-1
Merendino, K. A. II-112
Mersereau, W. A. II-151
Messina, E. J. II-176
Mestel, A. L. II-32
Meuli, J. II-208
Meyer, J. S. II-151
Mignone, R. J. II-214
Mikat, E. M. II-82
Milgrom, M. II-122
Millar, K. II-41, 151, 222
Miller, B. F. II-8, 152
Miller, B. L. II-75
Miller, H. A. II-108
Miller, I. D. II-138
Miller, L. H. II-88
Miller, R. A. II-109
Milnor, P., Jr. II-212
Mishra, S. II-22
Mitsouka, H. II-152
Miyauchi, Y. II-169
Mizukami, H. II-82, 152
Mobberley, M. L. II-23
Mody, M. R. II-153
Moellering, R. C., Jr. II-2
Mogabgab, W. J. II-61
Mohammed, I. II-197
Moller, J. H. II-197
Molnar, W. II-221
Molthan, L. II-75
Monheit, R. II-223
Monroe, R. G. II-153
Moor, G. F. II-218
Moore, D. II-153
Moore, S. II-151
Morales, A. R. II-118, 210
Morales, I. B. II-4
More, R. H. II-5, 17
Morgan, B. C. II-104, 154
Morgan, C. L. II-153
Morgan, D. Z. II-80
Morkin, E. II-99
Morris, J. D. II-157, 173
Morris, J. J., Jr. II-149, 154
Morrison, E. S. II-30
Morrison, J. T. II-115
Morrison, L. M. II-23
Morrow, A. G. II-58, 114, 179, 200, 205, 211
Morse, D. P. II-162, 173
Morton, W. E. II-155
Mosbach, E. H. II-31, 114
Moschos, C. B. II-155
Moser, K. M. II-55
Moses, M. L. II-155
Moss, A. J. II-156
Most, A. S. II-156
Moulder, P. V. II-73
Moutsos, S. E. II-156
Mowry, F. M. II-157
Mudd, J. G. II-157
Muller, B. F. II-43
Murata, K. II-23
Murphey, F. II-163
Murphree, O. D. II-179
Murphy, G. P. II-157
Murray, M. II-23
Mustard, J. F. II-19, 25
Mustard, W. T. II-124
Muster, A. J. II-158
Myers, H. J. II-203
Myers, J. L. II-180

N

Nadas, A. S. II-93, 117
Nadimi, M. II-217
Naeye, R. L. II-158
Nagano, S. II-102
Najmi, M. II-44
Nakao, K. II-159
Nakayama, R. II-159
Nakhjavan, F. K. II-159
Nassar, M. E. II-203
Nathan, D. II-161
Nathan, D. A. II-66, 159
Navab, A. II-148, 160
Navarro, R. U. II-49
Nazarian, I. H. II-34
Neill, W. A. II-160
Nelson, C. V. II-161
Nemir, P., Jr. II-161
Neufeld, H. N. II-161
Newman, B. J. II-131
Newman, H. A. I. II-24
Nichaman, M. Z. II-161
Nichol, E. S. II-24
Nichols, H. T. II-162
Nickerson, J. L. II-162
Niedermayer, W. II-162, 188
Niessen, N. E. II-48
Nieuwendijk, E. II-163
Nixon, C. W. II-45
Noble, R. P. II-25
Nofzinger, J. D. II-163
Nolan, J. P. II-163
Noonan, J. A. II-164, 177
Norman, J. C. II-164
Norton, E. W. D. II-74
Novack, P. II-102, 164, 199
Nugent, G. R. II-53
Numano, F. II-31
Nutter, D. O. II-146

O

Oka, M. II-159
Oken, D. E. II-165
Okin, J. T. II-102
Oldewurtel, H. A. II-106, 155
Oldham, H. N. II-211
Olson, A. C. II-25
Olson, R. E. II-189
Omura, Y. II-165
O'Neal, R. M. II-33
Onesti, G. II-166, 204
O'Reilly, R. A. II-166
Orejarena, H. II-64
Orgain, E. S. II-53, 85, 97, 128, 174
O'Rourke, R. A. II-72
Osborn, J. J. II-104, 113
Ottesen, O. E. II-44
Overy, H. R. II-102
Owen, C. A., Jr. II-224

P

Pacifico, A. D. II-136
Packham, M. A. II-25
Paden, J. T. II-134
Page, H. L., Jr. II-166
Page, I. H. II-4, 5, 27, 90
Page, L. B. II-167
Page, W. L. II-135
Paivio, A. II-176
Paley, H. W. II-167
Pallini, C. A. II-57, 167
Palmer, W. H. II-159
Pardo, A. II-116
Parker, B. M. II-168
Parlin, R. W. II-33
Parsonnet, V. II-49, 182
Parsons, W. B., Jr. II-26
Pascale, L. R. II-168, 215
Passovoy, M. II-64
Patel, D. J. II-169
Patman, R. D. II-207
Paton, B. C. II-169
Patterson, E. E. II-201
Patterson, J. L., Jr. II-179, 194
Pauk, G. L. II-133
Paul, M. H. II-158
Paulk, E. A., Jr. II-169
Pearce, C. W. II-170
Pearce, M. L. II-9
Pearson, J. II-208
Peckham, G. B. II-141
Peñaloza, D. II-79, 80, 205
Penneys, R. II-170

Pensinger, R. R. II-170
Perez-Stable, E. II-156
Perkins, W. H. II-76
Perley, A. M. II-141
Perloff, J. K. II-76
Peter, R. H. II-171
Peters, F. W. II-167
Peterson, D. R. II-156
Pevsner, H. II-162
Phillips, W. C. II-24
Phinney, A. O., Jr. II-171
Pick, A. II-135
Pick, R. II-6, 26
Pickard, H. A. II-176
Pierce, C. H. II-52
Pierie, W. II-171
Pierucci, L., Jr. II-155
Pietras, R. J. II-49, 103, 172
Pilkington, T. C. II-54
Pillsbury, R. C. II-139
Pina, R. II-159
Plonsey, R. II-172
Plotkin, F. H. II-110
Pollack, A. D. II-149
Poon-King, T. II-197
Popper, R. W. II-113, 177
Porter, G. A. II-172
Potter, E. V. II-197
Poutasse, E. F. II-97
Pressman, R. S. II-173
Preston, J. B. II-223
Preston, T. A. II-157, 173
Pritchard, W. H. II-128
Pritzker, C. R. II-30
Proudfit, W. L. II-173
Pryor, R. II-166, 221
Pryor, T. A. II-215
Puchner, T. C. II-33
Puiggari, M. J. II-103
Pur-Shahriari, A. A. II-73
Puyau, F. A. II-69

Q

Quilligan, J. J. II-23

R

Raab, W. II-174
Rabinowitz, D. II-126
Racine, P. II-187
Rackley, C. E. II-85, 174
Raghib, G. II-174
Rahimtoola, S. H. II-128
Rahmoeller, G. A. II-175
Raible, D. II-171
Rainey, R. L. II-175
Raley, E. M. II-105
Ramirez, O. II-204
Rams, J. J. II-73
Ranniger, K. II-73
Rapaport, E. II-124
Raper, A. J. II-179
Rasmussen, R. A. II-88
Rau, R. W. II-171
Read, R. C. II-159, 218
Rechnitzer, P. A. II-176
Redisch, W. II-176
Reed, W. A. II-176
Reemtsma, K. II-148
Reeve, R. II-177
Reeves, J. T. II-177
Regan, T. J. II-106, 217
Reid, J. M. II-120
Reinmuth, O. M. II-50
Renaud, S. II-27
Replogle, R. L. II-177
Reissell, P. K. II-17
Reynolds, E. W., Jr. II-43, 178
Reynolds, L. II-187
Riccardi, B. A. II-11
Richards, A. M. II-178
Richardson, D. W. II-179
Richardson, H. L. II-179
Rivera-Velez, J. M. II-128
Roberts, W. C. II-179
Robertson, A. L., Jr. II-5, 27
Robinson, B. F. II-91
Robinson, R. W. II-16, 21, 22, 27
Robinson, W. J. II-164
Roboz, J. II-221
Rochefort, J. G. II-10
Rodbard, S. II-28, 137
Rodriquez-Torres, R. II-140
Roe, B. B. II-180
Rolett, E. L. II-51, 52
Rosén, A. II-81, 115
Rosenbaum, J. L. II-180
Rosenberg, B. A. II-180
Rosenblum, R. II-181
Rosenfeld, R. S. II-28
Rosenquist, G. C. II-181
Ross, G. II-181
Ross, J., Jr. II-58, 71, 94, 127, 145
Ross, R. S. II-71
Rothfeld, E. L. II-49, 182
Rouse, J. II-149
Rowe, R. D. II-44, 59, 150, 182
Rowell, L. B. II-145, 183
Rowsell, H. C. II-19, 25
Rubinson, R. M. II-114
Rubinstein, R. A. II-34
Rudolph, A. M. II-74, 100, 113, 183
Ruiz, L. II-205
Ruiz, U. II-51
Runco, V. II-64, 136, 145, 183
Rushmer, R. F. II-184
Russell, H. E. II-184
Russell, R. P. II-184
Ruttenberg, H. D. II-120, 211
Ryan, J. M. II-135, 199, 221
Ryan, T. J. II-185

S

Sadd, J. R. II-185
Sager, R. V. II-87
Sako, Y. II-71
Saltzman, H. A. II-92, 185
Samet, P. II-186
Samuel, P. II-28, 29
Sanbar, S. S. II-29
Sances, A., Jr. II-131
Sandberg, H. II-12, 29
Sanders, C. A. II-186
Sandhu, R. S. II-120
Sandler, H. II-46, 109
Sanmarco, M. E. II-45
Sapirstein, L. A. II-186
Sarney, S. II-180
Sasahara, A. A. II-187
Satinsky, V. II-187
Saunders, J. C. II-11
Saunders, J. L. II-63
Scannell, J. G. II-187
Scanu, A. M. II-30
Scarpelli, E. M. II-100
Schaefer, J. II-162, 188
Schauf, V. II-34
Schechter, E. II-86
Scheinberg, P. II-50, 193
Schenk, E. II-156, 188
Schenker, V. II-203
Scheuer, J. II-56, 189
Schimert, G. II-92, 189
Schimke, R. N. II-149
Schirger, A. II-91, 130
Schirmer, H. K. II-157
Schjeide, O. A. II-23
Schloff, L. II-77
Schmid, P. G. II-189
Schmidt, M. II-114
Schmidt, P. J. II-114
Schmock, C. L. II-150
Schneck, D. J. II-190
Schnee, M. II-185
Schoenfeld, C. D. II-107
Schramel, R. II-170
Schrodt, G. R. II-23
Schuder, J. C. II-175
Schulz, K. J. II-63
Schumer, W. II-190
Schwartz, A. II-190
Schwartz, E. II-79
Schwartz, H. II-199
Schwartz, J. II-191
Schwartz, M. S. II-176
Schwartz, S. II-60
Schwarzkopf, H. J. II-162, 188
Schwedel, J. B. II-198
Schweitzer, M. D. II-48
Scolnick, E. M. II-30
Scott, H. M. II-81, 115
Scott, H. W., Jr. II-69, 203
Scott, J. B. II-74
Scott, R. F. II-30
Segal, B. L. II-44, 191
Segal, J. P. II-109
Segal, M. A. II-215
Seibert, R. A. II-190
Seiden, G. E. II-150
Sekulic, S. M. II-103
Sellers, R. D. II-93
Selzer, A. II-177, 191, 192

Selzer, B. II-94
Selzer, R. A. II-108
Semler, H. J. II-192
Serratto, M. II-109
Sevelius, G. II-103
Severino, J. II-205
Sewell, W. H. II-193
Sexton, R. R. II-74
Shafey, S. S. II-50, 193
Shah, P. M. II-193
Shaher, R. M. II-194
Shalchi, O. B. II-28, 29
Shapiro, A. P. II-156
Shapiro, S. II-87
Shapiro, W. II-194
Sharma, A. N. II-194
Shefer, S. II-31
Shepard, R. B. II-195
Sheps, S. G. II-90, 195, 209, 224
Sherf, L. II-118
Shimamoto, T. II-31
Shimojyo, S. II-50
Shirey, E. K. II-173
Shubin, H. II-196
Shultz, J. M. II-134
Shurtleff, D. II-121
Siegel, A. C. II-196
Siegel, J. H. II-196
Sieker, H. O. II-185
Sigmann, J. M. II-203
Silbert, M. II-142
Silbertrust, N. II-108
Sime, F. II-79, 205
Simmons, R. L. II-138, 197
Simon, N. M. II-197
Singer, D. H. II-197
Singh, S. II-213
Siposs, G. II-171
Sirak, H. D. II-221
Sjoerdsma, A. II-82
Skinner, J. J., Jr. II-121
Skinner, J. S. II-198
Sklar, H. II-198
Sloan, H. E. II-203
Smith, C. R. II-105
Smith, O. A., Jr. II-211
Smith, P. E. II-170
Smith, R. B. II-203
Smith, R. M. II-168
Smith, R. T. II-129, 198
Smith, W. W. II-92
Smulyan, H. II-19, 41, 66, 80
Snijder, J. II-79
Snyder, D. II-199
Snyder, J. R. II-199
Sodhi, H. S. II-31
Sokolow, M. II-32
Soloff, L. A. II-88, 199
Som, M. L. II-101
Sommer, L. S. II-200
Sommers, S. B. II-63
Sonnad, J. II-211
Sonnenblick, E. H. II-71, 145, 196, 200, 201
Sones, F. M., Jr. II-173
Soroff, H. S. II-51, 194, 200
Southworth, H. II-203
Spach, M. S. II-54, 85, 143
Spagnuolo, M. II-78, 83
Spain, D. M. II-32
Spann, J. F., Jr. II-201
Spector, A. A. II-32
Spittell, J. A., Jr. II-91
Spracklen, F. H. N. II-102
Spritz, N. II-201
Stanbaugh, G. H., Jr. II-201
Standish, M. S. II-35
Starbuck, W. C. II-190
Starr, A. II-54, 58, 127, 171, 172, 202
Stason, W. B. II-63
Stegall, H. F. II-184
Stein, E. II-126, 139
Stein, P. D. II-73, 202
Stein, W. G. II-77
Steinberg, D. II-32
Stephenson, S. E., Jr. II-203
Stern, A. M. II-203
Stilp, L. C., II II-99
Stinecipher, P. A. II-195
Stock, R. J. II-203
Stoeckle, H. II-175
Stollerman, G. H. II-196
Stoughton, P. V. II-171
Stout, C. II-15
Strauss, H. W. II-203
Stuckey, J. H. II-119, 203
Sullivan, J. M. II-204
Summers, N. D. II-129
Sun, S. C. II-61
Sundt, T. M. II-163
Sutton, G. C. II-208
Suzuki, L. II-15
Suzuki, M. II-33
Swan, H. J. C. II-75, 128
Swartz, C. D. II-166, 204
Swindall, B. T. II-74
Swyryd, E. A. II-15, 31

T

Takagi, M. II-218
Takagi, Y. II-151
Talbert, C. R., Jr. II-4
Talner, N. S. II-78
Tanney, H. II-11
Tanz, R. D. II-204
Tapia, F. A. II-80, 205
Taranta, A. II-78
Tarazi, R. C. II-90
Tatooles, C. J. II-205
Taylor, C. B. II-13, 22, 33
Taylor, C. W. II-190
Taylor, H. L. II-33, 178
Taylor, R. R. II-67
Taylor, W. J. II-139, 204
Teague, H. S. II-27
Tejada, C. II-116
Texter, E. C., Jr. II-206
Thal, A. P. II-44
Theilen, E. O. II-206
Theodore, H. C. II-33
Theogaraj, J. B. II-206
Thiers, R. E. II-149
Thomas, D. P. II-104, 207
Thomas, K. E. II-207
Thomas, W. A. II-21
Thompson, H. K., Jr. II-154
Thompson, J. E. II-207
Thorn, G. W. II-132, 133
Threefoot, S. A. II-208
Thrower, W. B. II-51
Tilney, N. II-62
Titus, J. L. II-84, 95
Tobian, L. II-208
Tobin, J. R., Jr. II-49, 103, 172, 208
Tokunaga, K. II-155
Tomitch, K. M. II-161
Toole, J. F. II-39, 69
Top, F. H., Jr. II-209
Torres, M. M. II-134
Tracy, R. E. II-34
Treger, A. II-102
Tremblay, G. M. II-187
Tsaltas, T. T. II-34
Tsuji, H. K. II-122
Tucker, R. M. II-209
Turner, D. F. II-220
Tursky, E. II-83
Tutor, F. T. II-98
Tweeddale, D. II-177
Tyce, G. M. II-195, 224
Tyson, R. R. II-210

U

Udenfriend, S. II-82
Udesen, H. II-162
Ulmer, F. II-162, 188
Unger, P. N. II-210
Urschel, H. C., Jr. II-210

V

Vagnucci, A. I. II-132, 133
Valdivia, E. II-211
Van Citters, R. L. II-144, 211
van Dam, R. Th. II-79
Van der Stichele, E. II-12, 29
van der Veen, K. II-163
Vannitamby, M. II-192
Varco, R. L. II-60, 65
Vasko, J. S. II-211
Vasquez, C. II-80
Vega, R. E. II-152
Velasco, C. A. II-64
Venezian, E. C. II-87
Vermeulen, F. II-14
Viamonte, M., Jr. II-212
Vichitbandha, P. II-140
Vick, R. L. II-190
Vincent, W. A. II-80
Vineberg, A. M. II-212
Vogel, J. H. K. II-70, 166, 212, 221
Vookles, J. T. II-212
Voudoukis, I. J. II-213

W

Wagenvoort, C. A. II-79
Wagner, D. E. II-161
Wagner, H. R. II-93
Wagner, R. P. II-141
Walker, W. G. II-213
Walker, W. J. II-213
Wallace, A. G. II-214
Wallace, H. W. II-214
Wallyn, R. J. II-168, 215
Wang, Y. II-215, 223
Wannamaker, L. W. II-209
Warden, H. E. II-207
Warner, E. D. II-18
Warner, H. II-12
Warner, H. R. II-215
Warren, J. V. II-107
Wasserman, A. J. II-194
Watanabe, Y. II-78
Waters, T. J. II-109
Watson, R. L. II-215
Webb, W. R. II-216
Weglicki, W. B. II-216
Weidman, W. H. II-113
Weil, M. H. II-57, 196
Weinberg, S. L. II-216
Weinblatt, E. II-87
Weinstein, L. II-57, 167
Weisse, A. B. II-217
Weissler, A. M. II-107
Wells, R. E. II-136, 217
Wendt, V. E. II-218
Werdegar, D. II-32
West, A. II-46
Westura, E. W. II-55
Weyn, A. S. II-218
Whalen, R. E. II-171, 174, 185, 216, 218
Wheat, M. II-71
Wheeler, C. G. II-207
Whereat, A. F. II-34
White, F. N. II-181, 219
White, K. L. II-96
White, R. I., Jr. II-71, 219
Whiter, H. H. II-95
Wigle, E. D. II-219
Williams, J. F., Jr. II-200, 220
Willman, V. L. II-121, 200
Wilson, G. T. T. II-88
Wilson, W. R. II-206
Wilson, W. S. II-196
Winbury, M. M. II-170, 220
Winkler, O. II-110
Winters, W. L., Jr. II-75
Wisoff, B. G. II-214
Wissler, R. W. II-88, 96, 220
Woldow, A. II-35
Wolf, L. E. II-117
Wolf, P. S. II-221
Wolf, R. L. II-221
Wolff, W. I. II-96, 101
Wolfman, M. II-98
Wolfman, R. M. II-119
Wong, M. II-124
Wood, J. A. II-202
Wooley, C. F. II-135, 183, 199, 221
Woolfolk, D. II-222
Woolverton, W. C. II-148
Wortman, B. II-30
Wylie, E. J. II-14
Wyllie, J. C. II-5, 17
Wyman, M. G. II-110

Y

Yacowitz, H. II-3
Yagi, H. II-49
Yagi, S. II-118, 222
Yalow, A. A. II-98
Yang, S. S. II-223
Yanowitz, F. II-223
Yao, A. C. II-140
Yardley, J. H. II-184
Yeh, T. J. II-103
Yormak, S. II-125
Younger, R. K. II-203
Yu, S. Y. II-35
Yuhasz, M. S. II-176

Z

Zierler, K. L. II-126
Zilversmit, D. B. II-24
Zimmerman, T. S. II-223
Zimon, R. P. II-224
Zinsser, H. F. II-224
Zoll, P. M. II-138
Zsoter, T. II-72
Zucker, I. R. II-49, 182
Zugibe, F. T. II-35
Zumoff, B. II-28
Zweifler, A. J. II-36

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Number Twelve

Five Congenital Cardiac Defects

A Study of the Profile and Natural History

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A Study of the Profile and Natural History

of

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ATRIAL SEPTAL DEFECT—PRIMUM TYPE
ATRIAL SEPTAL DEFECT—SECUNDUM TYPE
PULMONIC STENOSIS
VENTRICULAR SEPTAL DEFECT

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Contents

Foreword
James W. DuShane and William H. Weidman 1

Aortic Stenosis
Arno R. Hohn, Stella Van Praagh, A. A. Douglas Moore, Peter Vlad, and Edward C. Lambert 4

Atrial Septal Defect—Primum Type
Adrian S. Weyn, Stuart H. Bartle, Thomas B. Nolan, and J. Francis Dammann, Jr. 13

Atrial Septal Defect—Secundum Type
Alla G. Zaver and Alexander S. Nadas 24

Pulmonic Stenosis
O. Robert Levine and Sidney Blumenthal 33

Ventricular Septal Defect
Donald G. Ritter, Robert H. Feldt, William H. Weidman, and James W. DuShane 42

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